

09/139425
Att #14

1. Document ID: US 6180355 B1

L5: Entry 1 of 15

File: USPT

Jan 30, 2001

US-PAT-NO: 6180355

DOCUMENT-IDENTIFIER: US 6180355 B1

TITLE: Method for diagnosing and treating chronic pelvic pain syndrome

DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 435/7.1; 435/7.8

APPL-NO: 9/ 306927

DATE FILED: May 7, 1999

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION This application claims benefit of U.S. Provisional

Application No. 60/084,668, filed on May 7, 1998.

IN: Alexander, Richard B., Ponniah; Sathibalan

AB: The present invention provides a superior method of diagnosing Chronic Pelvic Pain Syndrome in men comprising measuring levels of cytokines in semen or components or fractions of semen. The invention also provides a method of treating a condition associated with elevated levels of a cytokine, such as TNF-.alpha., in semen or a component or fraction thereof, comprising administering a therapeutically effective amount of an ant-cytokine compound or composition, such as an anti-TNF-.alpha. compound or composition.

L5: Entry 1 of 15

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180355 B1

TITLE: Method for diagnosing and treating chronic pelvic pain syndrome

DETL: formation of prohormone fragment(s) by proteolysis of the mediated disease prohormone, and uses of the antibody including prophylactic and therapeutic methods to treat disease, and diagnostic assays for determining the amount of the prohormone and prohormone fragments present in a patients body. 5,700,909 Dec 23, Prosaposin and cytokine- Prosaposin and peptide derivatives derived therefrom will promote neurite outgrowth in 1997 derived peptides vitro. A peptide consensus sequence was determined by comparing the active neurite outgrowth-inducing saposin C peptide sequence with that of various hematopoietic and neuropoietic cytokines. These cytokine-derived peptides will promote the same processes as their corresponding cytokines. In addition, prosaposin and saposin C promote increased nerve cell myelination ex vivo. 5,700,788 Dec. 23, Ureido derivatives of Subject of the present invention are new ureido derivatives of naphthalenephosphonic 1997 naphthalenephosphonic acids having the following formula (I) [See Original Patent for Chemical Structure Diagram] acids (I) [See Original Patent for Chemical Structure Diagram] wherein each of m and n, which are the same, is an integer of 1 to 4; each of p and q, which are the same, is an integer of 1 to 3; and each of the R groups, which are the same, is a free or esterified phosphonic acid group; and the

pharmaceutically acceptable salts

thereof. 5,698,711 Dec. 16, Compounds containing This invention is directed to the pharmaceutical use of phenyl compounds, which are 1997 phenyl linked to aryl or linked to an aryl moiety by various linkages, for inhibiting tumor necrosis factor. The heteroaryl by an aliphatic- invention is also directed to the compounds, their preparation and pharmaceutical or heteroatom-containing compositions containing these compounds. Furthermore, this invention is directed to the linking group pharmaceutical use of the compounds for inhibiting cyclic AMP phosphodiesterase. 5,698,706 Dec. 16, Heterocyclic amides and Peptidyl derivatives having a SH or acyl S group and which are amides, primary amides or 1997 methods of use thioamides, have therapeutic utility via MMP or TNF inhibition. 5,698,579 Dec. 16, Cyclic amides Cyclic amides are inhibitors of tumor necrosis factor and can be used to combat cachexia, 1997 endotoxic shock, and retrovirus replication. A typical embodiment is 3-phenyl-3-(1- oxoisindolin-2-yl)propionamide. 5,698,564 Dec. 16, Diphenyl disulfide Diphenyl disulfide compounds having an inhibiting activity against the production of 1997 compounds Interleukin-1 beta (IL-1 beta) or the release of Tumor Necrosis Factor alpha (TNF alpha), which are useful in the treatment or prophylaxis of the diseases such as chronic rheumatism and sepsis are described. 5,698,518 Dec. 16, Method for regulating A method of treating patients to inhibit inflammation is disclosed. In the method, an 1997 inflammation and tumor effective amount of calmodulin, a calmodulin analogue or calmodulin receptor agonist is growth with calmodulin, administered to a patient to inhibit production of tumor necrosis factor and/or augment calmodulin analogues or elastase. In another method, an effective amount of calmodulin antagonist is administered calmodulin antagonists to a patient to stimulate immune response or inhibit elastase release. In another embodiment, a diagnostic test is disclosed to be used on patient blood samples to determine individual propensity to regulate tumor necrosis factor and/or elastase by calmodulin, its analogues or receptor agonists. 5,698,391 Dec 16, Methods for synthetic Methods useful for the determination of oligomers which have specific activity for a target 1997 unrandomization of molecule from a pool of primarily randomly assembled oligomers are provided. The oligomer fragments disclosed methods involve repeated syntheses of increasingly simplified sets of oligomers coupled with selection procedures for determining oligomers having the highest activity. Freedom from the use of enzymes allows the application of these methods to any molecules which can be oligomerized in a controlled fashion. 5,698,195 Dec. 16, Methods of treating Anti-TNF antibodies, fragments and regions thereof which are specific for human tumor 1997 rheumatoid arthritis using necrosis factor- alpha (TNF alpha) and are useful in vivo for diagnosis and therapy of a chimeric anti-TNF number of TNF alpha -mediated pathologies and conditions, including rheumatoid arthritis antibodies as well as polynucleotides coding for murine and chimeric antibodies, methods of producing the antibody, methods of use of the anti-TNF antibody, or fragment, region or derivative thereof, in immunoassays and immunotherapeutic approaches are provided. 5,695,993 Dec. 9, Cloning and regulation of Human protein C and activated protein C were shown to bind to endothelium specifically, 1997 an endothelial cell protein selectively and saturably (Kd = 30 nM, 7000 sites per cell) in a Ca<2 +> dependent C/activated protein C fashion. Expression

cloning revealed a 1.3

kb CDNA that coded for a novel type receptor transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR)

function and message are both down regulated by exposure of endothelium to TNF. Identification of

EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in

regulating the inflammatory response, and determination of methods for pharmaceutical use in

manipulating the inflammatory response. 5,695,953 Dec. 9, DNA that encodes a tumor Tumor Necrosis

Factor (TNF) Inhibitory Protein is isolated and substantially purified and 1997 necrosis factor

inhibitory the DNA that encodes the TNF inhibitory protein, vectors, host cells, and a

recombinant protein and a recombinant method for producing the encoded protein are also set

forth. It has the ability to inhibit: (a) method of production the binding of TNF to its

receptors, and (b) the cytotoxic effect of TNF. TNF Inhibitory Protein and salts, functional

derivatives and active fractions thereof can be used to antagonize the deleterious effects of

TNF. 5,691,382 Nov. 25, Inhibition of TNF production The present invention is directed to the

method of inhibiting the release of tumor necrosis 1997 with matrix factor (TNF) in a condition

mediated by TNF by administration of certain hydroxamic add metalloproteinase inhibitors

derivatives, also known as matrix metalloproteinase inhibitors, and thus the method of this

invention is useful in the management of diseases or conditions mediated by TNF. 5,691,381 Nov.

25, Hydroxamic and The present invention provides novel hydroxamic acids and carbocyclic acids

and 1997 carbocyclic acids as derivatives thereof and to pharmaceutical compositions and methods

of use of these novel metalloprotease inhibitors compounds for the inhibition of matrix

metalloproteinases, such as stromelysin, and inhibit the production of tumor necrosis factor

alpha, and for the treatment of arthritis and other related inflammatory diseases. these novel

compounds are represented by Formula I below [See Original Patent for Chemical Structure Diagram]

Formula I 5,688,805 Nov. 18, Tricyclic derivatives, Disclosed are compounds of Formula [See

Original Patent for Chemical Structure 1997 compositions and methods Diagram] (I) or a

pharmaceutically acceptable salt or solvate thereof. Also disclosed are of use pharmaceutical

compositions containing compounds of Formula I, methods for inhibiting tumor necrosis factor-

alpha and methods for treating septic shock, inflammation, or allergic disease. 5,686,455 Nov.

11, Imidazole derivatives and As cytokine inhibitors 2,4,5-triarylimidazole compounds and

compositions for use as 1997 their use as cytokine cytokine inhibitors. inhibitors 5,686,431 Nov.

11, Methods of using low The present invention relates to methods for the prevention and/or

treatment of 1997 molecular weight heparins pathological processes involving the induction of

TNF- alpha secretion comprising a for treatment of pathological pharmaceutically acceptable

carrier and a low molecular Weight heparin (LMWH). In the processes pharmaceutical compositions

of the present invention, the LMWH present in a low effective dose and is administered at

intervals of about 5-8 days. Furthermore, the LMWH is capable of inhibiting in vitro TNF- alpha

secretion by resting T cells and/or macrophages in response to T cell-specific antigens,

mitogens, macrophage activators, disrupted extracellular matrix (dECM),

laminin, fibronectin, and

the like. 5,686,259 Nov. 11, Assay method for the Cleavage site blocking antibody that binds to

prohormones, preferable Tumor Necrosis 1997 detection of 26 kd TNF Factor, thereby preventing the

formation of prohormone fragment(s) by proteolysis of the prohormone prohormone, and uses of the

antibody including prophylactic and therapeutic methods to treat disease, and diagnostic assays

for determining the amount of the prohormone and prohormone fragments present in a patients body.

5,684,222 Nov. 4, Mutant mouse having a The multiple biological activities of tumor necrosis

factor (TNF) are mediated by two 1997 disrupted TNFRp55 distinct cell surface receptors of 55 and

75 kDa. Mutant mice of the invention lacking tumor necrosis factor receptor (TNFR) p55 still

express functional TNFRp75 molecules at the cell surface. Normal weight and size of the mutant

mice are not altered. Thymocyte development and lymphocyte populations are normal, and clonal

deletion of potentially self-reactive T cells is not impaired. Activation of the nuclear

transcription factor kappa B (NF- kappa B), however, is completely abrogated after stimulation

with TNF. Moreover, TNFRp55 mutant mice are protected from septic shock induced by bacterial

endotoxin or superantigen, but Listeria clearance is severely impaired and mutant mice easily

succumb to Listeria infection. Thus, the two TNF receptors are not redundant, are independently

controlled, and play different roles in normal and pathological physiology. 5,679,696 Oct 21,

Compounds containing This invention is directed to the pharmaceutical use of phenyl compounds,

which are 1997 phenyl linked to aryl or linked to an aryl moiety by various linkages, for

inhibiting tumor necrosis factor. The heteroaryl by an aliphatic-or invention is also directed to

the compounds, their preparation and pharmaceutical heteroatom-containing compositions containing

these compounds. Furthermore, this invention is directed to the linking group pharmaceutical use

of the compounds for inhibiting cyclic AMP phosphodiesterase. 5,679,684 Oct. 21,

Hydroxyalkylammonium- Novel hydroxyalkylammonium-pyrimidine of the formula [See Original Patent

for Chemical 1997 pyrimidines and nucleoside Structure Diagram] (I) and nucleoside derivatives

have been found to be useful as derivatives, useful as inhibitors of inflammatory cytokines. They

can be used, inter alia, in the therapy of septic inhibitors of inflammatory shock, cachexia,

rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and cytokines AIDS. The

compounds are typically prepared by reaction of an iodo substituted nucleoside with the

appropriately

2. Document ID: US 6037450 A

L5: Entry 2 of 15

File: USPT

Mar 14, 2000

US-PAT-NO: 6037450

DOCUMENT-IDENTIFIER: US 6037450 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

DATE-ISSUED: March 14, 2000

US-CL-CURRENT: 530/350; 530/827, 530/830

APPL-NO: 9/ 082021

DATE FILED: May 20, 1998

PARENT-CASE:

This application is a divisional of U.S. Ser. No. 08/884,203, filed Jun. 27, 1997.

IN: Esmon; Charles T., Stearns-Kurosawa; Deborah J., Kurosawa; Shinichiro

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons and circulates at approximately 100 ng/ml (98.4 +/- 27.8 ng/ml, n=22). Plasma EPCR bound activated protein C with an affinity similar to that of recombinant soluble EPCR (K_d sub.app approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine. Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and appear to be correlated with inflammation and disease states associated with abnormal coagulation. Since EPCR expression is restricted to larger vessels and is usually negative in capillaries, these observations provide a mechanism for analyzing injury/stimulation of large vessel endothelial cells.

L5: Entry 2 of 15

File: USPT

Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6037450 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

BSPR:

The present invention is generally in the area of assays involving detection and/or measurement of endothelial cell protein C/activated protein C receptor or soluble forms thereof derived either by proteolysis or by alternative splicing.

BSPR:

EPCR is a recently identified receptor with significant homology to the CD1/MHC class I family (Fukudome and Esmon, 1994; Fukudome, et al. 1996. J. Biol. Chem. 271:17491-17498; Regan, et al. 1996. J. Biol. Chem. 271:17499-17503). The cloning and biological role of the endothelial cell receptor for protein C was described in PCT/US95/09636 by Oklahoma Medical Research Foundation, entitled "Cloning and Regulation of an Endothelial Cell Protein C/Activated Protein C Receptor". The protein was predicted to consist of 238 amino acids, which includes a 15 amino acid signal sequence at the N-terminus, and a 23 amino acid transmembrane region which characterizes the receptor as a type I transmembrane protein.

DEPR:

Endothelial Protein C Receptor, EPCR.

DEPC:

Identification of Functional Endothelial Protein C Receptor in Human Plasma

CLPR:

1. A modified endothelial protein C receptor having the structure of the protein defined by Seq. ID No. 2, residues 16-238 wherein the carboxyl terminal cysteine residue is replaced with another amino acid or is not palmitoylated.

CLPR:

2. The modified endothelial protein C receptor of claim 1 which is not glycosylated.

CLPR:

3. The modified endothelial protein C receptor of claim 1 further comprising a signal sequence having the structure of Seq. ID No. 2, residues 1-15.

CLPR:

4. The modified endothelial protein C receptor of claim 1 encoded by Seq. ID No. 1, or a nucleotide sequence hybridizing thereto under stringent conditions.

CLPR:

5. The modified endothelial protein C receptor of claim 4 encoded by Seq. ID No. 1.

CLPR:

6. The modified endothelial protein C receptor of claim 1 wherein the carboxyl terminal cysteine residue is replaced with another amino acid.

CLPR:

7. The modified endothelial protein C receptor of claim 1 wherein the carboxyl terminal cysteine residue is not palmitoylated.

CLPR:

8. The modified endothelial protein C receptor of claim 1 which is human endothelial protein C receptor except for the modification.

CLPR:

9. An isolated naturally occurring alternatively spliced endothelial protein C receptor present in plasma having the structure defined by Seq. ID No. 2, further comprising a protein insert after Gly 201.

CLPR:

10. The isolated naturally occurring alternatively spliced endothelial protein C receptor of claim 9 comprising protein inserts as shown in FIG. 3.

CLPR:

11. An isolated naturally occurring soluble endothelial protein C receptor having the structure of Seq. ID No. 2, residues 16-201, wherein the receptor has been cleaved at a naturally occurring proteolytic cleavage site before the transmembrane domain present in plasma.

CLPR:

12. The isolated naturally occurring soluble endothelial protein C receptor of claim 11 encoded by a DNA sequence hybridizing to Seq. ID No. 1 under stringent conditions.

ORPL:

Kurosawa, et al., "Identification of functional Endothelial Protein C Receptor in Human Plasma," J. Clin. Invest. 100(2): 411-418 (1997).

ORPL:

Fukudome and Esmon, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell Protein C/Activated Protein C Receptor (EPCR)--The Structural and

Functional Conservation in

Human, Bovine and Murine EPCR*, "J. Biol. Chem. 270(10):5571-5577 (1995).

ORPL:

Laszik, et al., "The Human Protein C Receptor Is Present Primarily on Endothelium of Large Blood Vessels," Circulation, 96(10):1-9 (1997).

ORPL:

Regan, et al., "The Endothelial Cell Protein C Receptor--Inhibition of Activated Protein C Anticoagulant Function without Modulation of Reaction with Proteinase Inhibitors*," J. Biol. Chem. 271(29):17499-17503 (1996).

ORPL:

Steams-Kurosawa, et al., "The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex," Proc. Nation Acad. Sci. (USA) 93:10212-10216 (1996).

3. Document ID: US 5852171 A

L5: Entry 3 of 15

File: USPT

Dec 22, 1998

US-PAT-NO: 5852171

DOCUMENT-IDENTIFIER: US 5852171 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DATE-ISSUED: December 22, 1998

US-CL-CURRENT: 530/350; 530/380

APPL-NO: 8/ 878283

DATE FILED: June 18, 1997

PARENT-CASE:

This is a divisional of U.S. Ser. No. 08/289,699, filed on Aug. 12, 1994, now U.S. Pat. No. 5,695,993.

IN: Fukudome; Kenji; Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{+2} dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L5: Entry 3 of 15

File: USPT

Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5852171 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

ABPL:

Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{+2} dependent fashion.

Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

BSPR:

The present invention is generally in the area of cloning, expression, and regulation of an endothelial cell protein C/activated protein C receptor.

DEPR:

Expression cloning revealed a 1.3 kb cDNA that coded for a type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily.

Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF.

Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of this receptor for protein C in regulating the inflammatory response.

DEPR:

The identification of the protein C receptor on endothelium suggests that the endothelial cell binds protein C/APC through three distinct mechanisms. In addition to EPCR, protein S can bind APC/protein C on negatively charged membrane surfaces that include the endothelium (Stern et al., (1986) J. Biol. Chem. 261, 713-718), but this is not cell type specific (Dahlback et al., 1992).

Thrombomodulin in complex with thrombin can bind protein C and APC (Hogg et al., 1992). On endothelium, the protein S binding sites (Navroth and Stern, (1986) J. Exp. Med. 163, 740-745), thrombomodulin (Esmon, 1989) and EPCR are all down regulated by cytokines, indicating that inflammation can impair protein C pathway function at multiple levels.

DEPR:

As described herein, a variety of compounds can be used to inhibit or enhance expression of the EPCR. The nature of the disorder will determine if the expression should be enhanced or inhibited. For example, based on the studies involving the use of an anti-protein C antibody in combination with cytokine, it should be possible to treat solid tumors by enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor by administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis, stroke, thrombosis, septic shock, adult respiratory distress syndrome, and

pulmonary emboli using
a method for inhibiting an inflammatory response involving administration of EPCR or EPCR fragments or substances that upregulate EPCR expression to a patient in need of treatment thereof.

CLPR:

1. An isolated endothelial cell protein C/activated protein C receptor having the amino acid sequence of Sequence ID No. 2 or a sequence having conservative substitutions, additions or deletions thereof, having functionally equivalent receptor binding activity to activated Protein C.

4. Document ID: US 5804392 A

L5: Entry 4 of 15

File: USPT

Sep 8, 1998

US-PAT-NO: 5804392

DOCUMENT-IDENTIFIER: US 5804392 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

DATE-ISSUED: September 8, 1998

US-CL-CURRENT: 435/7.1; 435/7.8, 435/975, 436/506, 530/387.1, 530/388.22, 530/389.1

APPL-NO: 8/ 884203

DATE FILED: June 27, 1997

IN: Esmon; Charles T., Stearns-Kurosawa; Deborah J., Kurosawa; Shinichiro

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons and circulates at approximately 100 ng/ml (98.4 +/- 27.8 ng/ml, n=22). Plasma EPCR bound activated protein C with an affinity similar to that of recombinant soluble EPCR (Kd.sub.app approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine.

Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and appear to be correlated with inflammation and disease states associated with abnormal coagulation. Since EPCR expression is restricted to larger vessels and is usually negative in capillaries, these observations provide a mechanism for analyzing injury/stimulation of large vessel endothelial cells.

L5: Entry 4 of 15

File: USPT

Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804392 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

BSPR:

The present invention is generally in the area of assays involving detection and/or measurement of endothelial cell protein C/activated protein C receptor or soluble forms thereof derived either by proteolysis or by alternative splicing.

BSPR:

EPCR is a recently identified receptor with significant homology to the CD1/MHC class I family (Fukudome and Esmon, 1994; Fukudome, et al. 1996. J. Biol. Chem. 271:17491-17498; Regan, et al. 1996. J. Biol. Chem. 271:17499-17503). The cloning and biological role of the endothelial cell receptor for protein C was described in PCT/US95/09636 by Oklahoma Medical Research Foundation, entitled "Cloning and Regulation of an Endothelial Cell Protein C/Activated Protein C Receptor". The protein was predicted to consist of 238 amino acids, which includes a 15 amino acid signal sequence at the N-terminus, and a 23 amino acid transmembrane region which characterizes the receptor as a type I transmembrane protein.

DEPR:

Endothelial Protein C Receptor, EPCR.

DEPC:

Identification of Functional Endothelial Protein C Receptor in Human Plasma

CLPR:

1. An assay for soluble endothelial protein C receptor comprising

CLPR:

3. The assay of claim 1 further comprising the step of correlating the amount of soluble endothelial protein C receptor with calibration standards.

CLPR:

8. A kit for detection and measurement of endothelial protein C receptor comprising

CLPR:

9. The kit of claim 8 where the antibody has a higher affinity for endothelial protein C receptor including the transmembrane domain than for endothelial protein C receptor not including the transmembrane domain.

CLPR:

10. The kit of claim 8 wherein the antibody is immunoreactive with the insert in an alternatively spliced endothelial protein C receptor.

CLPR:

11. The kit of claim 8 wherein the antibodies block binding of endothelial protein C receptor and activated protein C or protein C.

CLPV:

measuring the amount of soluble endothelial protein C receptor.

CLPV:

an antibody immunoreactive with endothelial protein C receptor,

CLPV:

reagents to detect a reaction between the antibody and endothelial protein C receptor in a sample from a patient, and

CLPV:

standards to correlate the amount of reaction to normal and abnormal levels of endothelial

protein C receptor.

ORPL:

Fukudome, et al., "The Endothelial Cell Protein C Receptor--Cell Surface Expression and Direct Ligand Binding by the Soluble Receptor," J. Biol. Chem. 271(29):17491-17498 (1996).

ORPL:

Fukudome and Esmon, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell Protein C/Activated Protein C Receptor (EPCR)--The Structural and Functional Conservation in Human, Bovine and Murine EPCR*," J. Biol. Chem. 270(10):5571-5577 (1995).

ORPL:

Regan, et al., "The Endothelial Cell Protein C Receptor--Inhibition of Activated Protein C Anticoagulant Function without Modulation of Reaction with Proteinase Inhibitors*," J. Biol. Chem. 271(29):17499-17503 (1996).

5. Document ID: US 5695993 A

L5: Entry 5 of 15

File: USPT

Dec 9, 1997

US-PAT-NO: 5695993

DOCUMENT-IDENTIFIER: US 5695993 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/325; 435/320.1, 435/69.1, 536/23.5

APPL-NO: 8/ 289699

DATE FILED: August 12, 1994

IN: Fukudome; Kenji, Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L5: Entry 5 of 15

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated

protein C receptor

ABPL:

Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion.

Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

BSPR:

The present invention is generally in the area of cloning, expression, and regulation of an endothelial cell protein C/activated protein C receptor.

DEPR:

Expression cloning revealed a 1.3 kb cDNA that coded for a type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily.

Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF.

Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of this receptor for protein C in regulating the inflammatory response.

DEPR:

The identification of the protein C receptor on endothelium suggests that the endothelial cell binds protein C/APC through three distinct mechanisms. In addition to EPCR, protein S can bind APC/protein C on negatively charged membrane surfaces that include the endothelium (Stern et al., (1986) J. Biol. Chem. 261, 713-718), but this is not cell type specific (Dahlback et al., 1992).

Thrombomodulin in complex with thrombin can bind protein C and APC (Hogg et al., 1992). On endothelium, the protein S binding sites (Nawroth and Stern, (1986) J. Exp. Med. 163, 740-745), thrombomodulin (Esmon, 1989) and EPCR are all down regulated by cytokines, indicating that inflammation can impair protein C pathway function at multiple levels.

DEPR:

As described herein, a variety of compounds can be used to inhibit or enhance expression of the EPCR. The nature of the disorder will determine if the expression should be enhanced or inhibited. For example, based on the studies involving the use of an anti-protein C antibody in combination with cytokine, it should be possible to treat solid tumors by enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor by administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis, stroke, thrombosis, septic shock, adult respiratory distress syndrome, and pulmonary emboli using a method for inhibiting an inflammatory response involving administration of EPCR or EPCR

fragments or substances that upregulate EPCR expression to a patient in need of treatment thereof.

File: USPT

Sep 9, 1997

CLPR:

6. An isolated nucleic acid molecule as set forth in SEQ ID No. 1 encoding an endothelial cell protein C/activated protein C receptor protein.

ORPL:

Fukudome, K. et al., "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell Protein C/activated Protein C Receptor (EPCR)", J. Biological Chemistry, vol. 270, no. 10, pp. 5571-5577 (1995).

ORPL:

Fukudome, K. et al., "Identification, Cloning, and Regulation of Novel Endothelial Cell Protein C/activated Protein C Receptor", Circulation, vol. 90, no. 4, pt. 2, pp. I-N, 1133 (1994).

ORPL:

Fukudome, K. et al., "Identification, Cloning, and Regulation of Novel Endothelial Cell Protein C/activated Protein C Receptor", J. Biological Chemistry, vol. 269, No. 42, pp. 26486-26491 (1994).

DOCUMENT-IDENTIFIER: US 5665556 A

TITLE: Complement components and binding ligands in fertility

DEPR:

This invention is based on the recognition by the inventors that acrosome-reacted sperm bound to a mAb (H316) directed to a trophoblast cell surface antigen, and that the same antigen, present on leucocytes as well, was identical to a C binding protein, gp45-70, also known as the membrane cofactor protein (MCP). The antigen identified by the H316 mAb which is identical to MCP is also the same as the HuLy-m5 antigen (Johnson, P. M. et al., in: Reproductive Immunology 1989, Mettler & Billington (eds.), Elsevier, Amsterdam (in press). Under the current system of nomenclature, this antigen has been designated CD46. As a result of this discovery, the inventors conceived of a role for MCP, as a C binding protein or a C receptor (CR) on the surface of gametes, in the process of sperm-egg interaction during the fertilization process. The invention is therefore directed to the exploitation of the presence of this CR on gametes in the diagnosis of infertility, in the identification and isolation of acrosome-reacted sperm, in the promotion or inhibition of fertilization in vitro or in vivo, and in the treatment of infertility.

6. Document ID: US 5665556 A

L5: Entry 6 of 15

File: USPT

Sep 9, 1997

US-PAT-NO: 5665556

DOCUMENT-IDENTIFIER: US 5665556 A

TITLE: Complement components and binding ligands in fertility

DATE-ISSUED: September 9, 1997

US-CL-CURRENT: 435/7.21; 435/2, 435/7.2, 435/806, 436/510, 436/518, 436/519, 436/65, 436/821, 436/906, 530/852

APPL-NO: 8/ 441067

DATE FILED: May 15, 1995

PARENT-CASE:

This application is a continuation application of U.S. application Ser. No. 08/137,820, filed

Oct. 19, 1993, now U.S. Pat. No. 5,474,927, which is a continuation application of U.S.

application Ser. No. 07/487,039, filed Mar. 2, 1990, now abandoned.

IN: Anderson; Deborah J., Johnson; Peter M., Jack; Richard M.

AB: Methods for detecting and isolating acrosome-reacted sperm and complement receptor-bearing oocytes using the complement component C3, fragments, or variants thereof, antibodies to a complement receptor, or antibodies to C3, are disclosed. These methods have application in the assessment of fertility, in the preparation of sperm or oocytes for in vitro fertilization or for gamete intrafallopian tube transfer, in promoting or inhibiting fertilization in vitro and in vivo, and in diagnosing and treating infertility.

L5: Entry 6 of 15

7. Document ID: US 5474927 A

L5: Entry 7 of 15

File: USPT

Dec 12, 1995

US-PAT-NO: 5474927

DOCUMENT-IDENTIFIER: US 5474927 A

TITLE: Complement components and binding ligands in fertility

DATE-ISSUED: December 12, 1995

US-CL-CURRENT: 435/7.21; 435/806, 436/510, 436/519, 436/65, 436/821, 436/906

APPL-NO: 8/ 137820

DATE FILED: October 19, 1993

PARENT-CASE:

This application is a continuation of application Ser. No. 07/487,039, filed Mar. 2, 1990, abandoned.

IN: Anderson; Deborah J., Johnson; Peter M., Jack; Richard M.

AB: Methods for detecting and isolating acrosome-reacted sperm and complement receptor-bearing oocytes using the complement component C3, fragments, or variants thereof, antibodies to a complement receptor, or antibodies to C3, are disclosed. These methods have application in the assessment of fertility, in the preparation of sperm or oocytes for in vitro fertilization or for gamete intrafallopian tube transfer, in promoting or inhibiting fertilization in vitro and in vivo, and in diagnosing and treating infertility.

L5: Entry 7 of 15

File: USPT

Dec 12, 1995

DOCUMENT-IDENTIFIER: US 5474927 A

TITLE: Complement components and binding ligands in fertility

DEPR:

This invention is based on the recognition by the inventors that acrosome-reacted sperm bound to a mAb (H316) directed to a trophoblast cell surface antigen, and that the same antigen, present on leucocytes as well, was identical to a C binding protein, gp45-70, also known as the membrane cofactor protein (MCP). The antigen identified by the H316 mAb which is identical to MCP is also the same as the HuLy-m5 antigen (Johnson, P. M. et al., in: Reproductive Immunology 1989, Mettler & Billington (eds.), Elsevier, Amsterdam (in press). Under the current system of nomenclature, this antigen has been designated CD46. As a result of this discovery, the inventors conceived of a role for MCP, as a C binding protein or a C receptor (CR) on the surface of gametes, in the process of sperm-egg interaction during the fertilization process. The invention is therefore directed to the exploitation of the presence of this CR on gametes in the diagnosis of infertility, in the identification and isolation of acrosome-reacted sperm, in the promotion or inhibition of fertilization in vitro or in vivo, and in the treatment of infertility.

8. Document ID: US 5804392 A

L5: Entry 8 of 15

File: EPAB

Sep 8, 1998

PUB-NO: US005804392A

DOCUMENT-IDENTIFIER: US 5804392 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

PUBN-DATE: September 8, 1998

INT-CL (IPC): G01N 33/53; G01N 33/564; C07K 16/28

APPL-NO: US88420397

APPL-DATE: June 27, 1997

PRIORITY-DATA:

IN: ESMON, CHARLES T, STEARNS-KUROSAWA, DEBORAH J, KUROSAWA, SHINICHIRO

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons and circulates at approximately 100 ng/ml (98.4 +/- 27.8 ng/ml, n=22). Plasma EPCR bound activated protein C with an affinity similar to that of recombinant soluble EPCR (Kdapp approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage factor Xa clotting assay.

Soluble plasma EPCR

appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine.

Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and appear to be correlated with inflammation and disease states associated with abnormal coagulation. Since EPCR expression is restricted to larger vessels and is usually negative in capillaries, these observations provide a mechanism for analyzing injury/stimulation of large vessel endothelial cells.

L5: Entry 8 of 15

File: EPAB

Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804392 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

9. Document ID: US 5695993 A

L5: Entry 9 of 15

File: EPAB

Dec 9, 1997

PUB-NO: US005695993A

DOCUMENT-IDENTIFIER: US 5695993 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

PUBN-DATE: December 9, 1997

INT-CL (IPC): C12N 5/16; C07H 21/04

EUR-CL (EPC): C07K014/705

APPL-NO: US28969994

APPL-DATE: August 12, 1994

PRIORITY-DATA:

IN: FUKUDOME, KENJI, ESMON, CHARLES T

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L5: Entry 9 of 15

File: EPAB

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

FPAR:
Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{2+} dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

10. Document ID: WO 9605303 A1

L5: Entry 10 of 15

File: EPAB

Feb 22, 1996

PUB-NO: WO009605303A1
DOCUMENT-IDENTIFIER: WO 9605303 A1
TITLE: CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ACTIVATED PROTEIN C RECEPTOR

PUBN-DATE: February 22, 1996

INT-CL (IPC): C12N 15/12; C07K 14/705; A61K 39/395; C12N 15/11; A61K 38/17; C07K 16/28; G01N 33/68
EUR-CL (EPC): C07K014/705

APPL-NO: US09509636
APPL-DATE: August 9, 1995

PRIORITY-DATA:

IN: FUKUDOME, KENJI, ESMON, CHARLES T

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{2+} dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in

regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L5: Entry 10 of 15

File: EPAB

Feb 22, 1996

DOCUMENT-IDENTIFIER: WO 9605303 A1
TITLE: CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ACTIVATED PROTEIN C RECEPTOR

FPAR:
Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{2+} dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

11. Document ID: US 6037450 A

L5: Entry 11 of 15

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-246200
DERWENT-WEEK: 200023
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Modified endothelial protein C receptor, useful as diagnostic marker of e.g. inflammation or autoimmune diseases, is a soluble or alternatively spliced form of the receptor

PRIORITY-DATA: 1997US-0884203 (June 27, 1997), 1998US-0082021 (May 20, 1998)

PATENT-FAMILY:
PUB-NO

PUB-DATE	LANGUAGE	PAGES
US 6037450 A	MAIN-IPC	
March 14, 2000		
N/A		024
		C07K014/705

APPLICATION-DATA:		
PUB-NO	APPL-DATE	APPL-NO
		DESCRIPTOR
US 6037450A		

June 27, 1997

1997US-0884203

Div ex

US 6037450A

May 20, 1998

1998US-0082021

N/A

INT-CL (IPC): C07K 14/705

IN: ESMON, C T, KUROSAWA, S, STEARNS-KUROSAWA, D J

AB: NOVELTY - Modified endothelial protein C receptor (I) comprises amino acids (aa) 16-238 of a 238 aa sequence (S2) given in the specification, and has the C-terminal Cys replaced by some other aa, or is not palmitoylated., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) isolated, natural alternatively spliced form (1a) of (I), comprising (S2) with a protein insertion after Gly 201; and, (2) isolated, natural form (1b) of (I) comprising residues 16-201 of (S2) that has been cleaved, in plasma, at a protease site before the transmembrane domain., ACTIVITY - None given., MECHANISM OF ACTION - (I) blocks activation of cellular protein C and anticoagulant activity of activated protein C., USE - (I) blocks activation of cellular protein C and anticoagulant activity of activated protein C. Measurement of (I), in standard immunoassays, is used to diagnose disorders involving coagulation or inflammation, or autoimmune diseases (e.g. lupus erythematosus; sepsis; diabetes; pre-eclampsia; restenosis and many others) also for monitoring treatment. (I) is a marker of endothelial cells so its presence may also indicate damage to large blood vessels, e.g. drug-induced damage. The antibodies used for immunoassay may also be used to characterize and isolate receptor proteins and to modulate receptor protein activity, particularly to inhibit binding to ligands.

L5: Entry 11 of 15

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-246200

DERWENT-WEEK: 200023

COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Modified endothelial protein C receptor, useful as diagnostic marker of e.g. inflammation or autoimmune diseases, is a soluble or alternatively spliced form of the receptor

ABTX:

NOVELTY - Modified endothelial protein C receptor (I) comprises amino acids (aa) 16-238 of a 238 aa sequence (S2) given in the specification, and has the C-terminal Cys replaced by some other aa, or is not palmitoylated.

12. Document ID: AU 9959013 A, WO 200010609 A1

L5: Entry 12 of 15

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-224557

DERWENT-WEEK: 200031

COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or diagnosis of cardiovascular disease, by targeting the endothelial cell protein-C receptor

PRIORITY-DATA: 1998US-0139425 (August 25, 1998)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

AU 9959013 A

March 14, 2000

N/A

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A61K045/06

WO 200010609 A1

March 2, 2000

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023

A61K045/06

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

AU 9959013A

August 25, 1999

1999AU-0059013

N/A

AU 9959013A

WO 200010609

Based on

WO 200010609A1

August 25, 1999

1999WO-US19480

N/A

INT-CL (IPC): A61K 45/06

IN: ESMON, C T, XU, J

AB: NOVELTY - A method of selectively delivering molecules (I) to the nucleus of endothelial cells of large vessels by administering a conjugate (C) of (I) with an agent (II) that binds selectively to endothelial protein C receptor (EPCR)., DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not a diagnostic label, with either protein C, optionally activated, or an antibody reactive with EPCR, or fragments of it which bind EPCR., ACTIVITY - Antithrombotic; fibrinolytic; antiinflammatory; anticoagulant; vasoconstrictor., MECHANISM OF ACTION - EPCR translocates from the plasma membrane to the nucleus, and transports molecules that bind to it., USE - (C) are used to deliver therapeutic agents, e.g. nucleic acids, proteins, expression inhibitors, anti-inflammatories, anticoagulants, growth hormones etc., or diagnostic agents such as radiolabels, fluorescent labels and enzymatic labels, particularly in the cases of cardiovascular disease. Typical applications include preventing thrombosis, increasing fibrinolytic activity, or inhibiting leukocyte adhesion., ADVANTAGE - Since EPCR is present mainly on endothelial cells of large vessels, rather than similar cells in

capillaries or
other small vessels, especially in arteries, using it as target provides
selective delivery
of (I) with reduced risks of systemic complications. Serum stimulates
nuclear translocation
of EPCR, so delivery is enhanced during inflammatory or coagulative
processes, often present
in the treated subjects.

L5: Entry 12 of 15

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful
for treatment or
diagnosis of cardiovascular disease, by targeting the endothelial cell
protein C receptor

ABTX:
NOVELTY - A method of selectively delivering molecules (I) to the
nucleus of endothelial cells of
large vessels by administering a conjugate (C) of (I) with an agent (II) that
binds selectively
to endothelial protein C receptor (EPCR).

13. Document ID: US 5804392 A, WO 9900673 A1, AU 9882694 A,
EP 991946 A1
L5: Entry 13 of 15

File: DWPI

Sep 8, 1998

DERWENT-ACC-NO: 1998-505645
DERWENT-WEEK: 200023
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Immuno-based detection of protein C receptor - useful in the
diagnosis of inflammatory and
coagulation states and disorders associated with damage to endothelium
and large blood vessel
disease

PRIORITY-DATA: 1997US-0884203 (June 27, 1997)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

US 5804392 A

September 8, 1998

N/A

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G01N033/53

WO 9900673 A1

January 7, 1999

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G01N033/68

AU 9882694 A

January 19, 1999

N/A

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G01N033/68

EP 991946 A1

April 12, 2000

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G01N033/68

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

US 5804392A

June 27, 1997

1997US-0884203

N/A

WO 9900673A1

June 26, 1998

1998WO-US13385

N/A

AU 9882694A

June 26, 1998

1998AU-0082694

N/A

AU 9882694A

WO 9900673

Based on

EP 991946A1

June 26, 1998

1998EP-0932912

N/A

EP 991946A1

June 26, 1998

1998WO-US13385

N/A

EP 991946A1

WO 9900673

Based on

INT-CL (IPC): C07K 14/705; C07K 16/28; G01N 33/53; G01N 33/564;
G01N 33/68

IN: ESMON, C T, KUROSAWA, S, STEARNS-KUROSAWA, D J

AB: An assay for soluble endothelial protein C receptor comprises
containing a,
sample from a patient to be tested and measuring the amount of soluble
endothelial protein C
receptor., Also claimed is a kit for detection and measurement of
endothelial protein C
receptor comprising:., (a) an antibody immunoreactive with endothelial
protein C receptor;.,
(b) reagents to detect a reaction between the Ab and endothelial protein C
receptor in a
patient sample; and, (c) standards to correlate the amount of reaction to
normal and
abnormal levels of endothelial protein C receptor., USE - The assay is
used for the
diagnosis of coagulation and inflammatory states and disorders, damage
to endothelium, and
large blood vessel disease, e.g. autoimmune diseases, transplantation,
sepsis, shock,
pre-eclampsia, diabetes, vascular disease (especially cardiopulmonary
bypass, unstable
angina, restenosis and angioplasty), kidney disease and liver disease
(claimed). Protein C
is involved in the regulation of a host response to inflammation. The
protein is one of the
last components to be activated in the coagulation system, and is thought
to control
coagulation and inflammation. Activation of the receptor through a
pathway involving
thrombin, activates protein C. The protein C pathway is apparently only
involved in large
blood vessels, not capillaries, and so is activated with for major vascular
conditions, and
the increased presence of the receptor in the conditions stated makes it
ideal as a

diagnostic component.

L5: Entry 13 of 15

File: DWPI

Sep 8, 1998

DERWENT-ACC-NO: 1998-505645
DERWENT-WEEK: 200023
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Immuno-based detection of protein C receptor - useful in the diagnosis of inflammatory and coagulation states and disorders associated with damage to endothelium and large blood vessel disease

ABTX:

An assay for soluble endothelial protein C receptor comprises containing a

ABTX:

sample from a patient to be tested and measuring the amount of soluble endothelial protein C receptor.

ABTX:

Also claimed is a kit for detection and measurement of endothelial protein C receptor comprising:

ABTX:

(a) an antibody immunoreactive with endothelial protein C receptor;

ABTX:

(b) reagents to detect a reaction between the Ab and endothelial protein C receptor in a patient sample; and

ABTX:

(c) standards to correlate the amount of reaction to normal and abnormal levels of endothelial protein C receptor.

14. Document ID: AU 719629 B, WO 9820041 A1, AU 9854317 A, EP 937104 A1

L5: Entry 14 of 15

File: DWPI

May 11, 2000

DERWENT-ACC-NO: 1998-286871
DERWENT-WEEK: 200031
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TITLE: Regulatory elements from the endothelial protein C receptor promoter - useful to direct expression of genes or nucleotide molecules e.g. to endothelial cells or only large vessel endothelial cells in gene therapy

PRIORITY-DATA: 1997US-0054533 (August 4, 1997), 1996US-0030718 (November 8, 1996)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

AU 719629 B

May 11, 2000

N/A

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C07K014/705

WO 9820041 A1

May 14, 1998

E

069

C07K014/705

AU 9854317 A

May 29, 1998

N/A

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C07K014/705

EP 937104 A1

August 25, 1999

E

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C07K014/705

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

AU 719629B

November 7, 1997

1998AU-0054317

N/A

AU 719629B

AU 9854317

Previous Publ.

AU 719629B

WO 9820041

Based on

WO 9820041A1

November 7, 1997

1997WO-US20364

N/A

AU 9854317A

November 7, 1997

1998AU-0054317

N/A

AU 9854317A

WO 9820041

Based on

EP 937104A1

November 7, 1997

1997EP-0948205

N/A

EP 937104A1

November 7, 1997

1997WO-US20364

N/A

EP 937104A1

WO 9820041

Based on

INT-CL (IPC): C07H 21/04; C07K 14/705; C12N 15/12

IN: ESMON, C T, GU, J

AB: Regulatory elements (I) isolated from the endothelial protein C receptor (EPCR) promoter which directs expression selectively to endothelial cells are new. Also claimed are constructs for heterologous gene expression comprising (I), USE - The regulatory elements are useful to control expression of a gene/biologically active nucleotide molecule (claimed), by expressing these under control of one of the elements (optionally with the thrombin response element) (claimed). Expression of the gene/nucleotide molecule is selectively in large vessel endothelial cells and/or as a result of environmental stimuli (either thrombin or serum) can be achieved by inclusion of the appropriate

regulatory element(s). Atherosclerosis and most other vascular diseases primarily occur in large vessels, and for gene therapy for such diseases it is desirable to target endothelial cells, the primary defence mechanism against cellular infiltration and thrombosis. The constructs are therefore particularly useful in gene therapy, especially when the gene encodes a protein, or the nucleotide molecules are antisense, triplex forming, ribozymes or guide sequences for RNAase P (claimed) which are used to mutate or stop transcription of a particular gene. Such genes/nucleotide molecules may be expressed in vivo in patients or in cell culture (claimed). For example, endothelial response elements may be used for any gene therapy where systemic distribution is required, whilst large vessel endothelial cell response elements are useful for expression of thrombomodulin in large vessel endothelium to decrease clot propensity at atheromas or in autoimmune diseases; the environmental stimuli response element(s) are useful e.g. to deliver agents whose expression should be increased during increased thrombin/platelet activation or regional trauma. The regulatory elements are also useful as hybridisation probes, in increasing expression of recombinant proteins by exposure of the encoding construct to thrombin and in drug screening and design (not claimed).

L5: Entry 14 of 15

File: DWPI

May 11, 2000

DERWENT-ACC-NO: 1998-286871

DERWENT-WEEK: 200031

COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Regulatory elements from the endothelial protein C receptor promoter - useful to direct expression of genes or nucleotide molecules e.g. to endothelial cells or only large vessel endothelial cells in gene therapy

ABTX:

Regulatory elements (I) isolated from the endothelial protein C receptor (EPCR) promoter which directs expression selectively to endothelial cells are new. Also claimed are constructs for heterologous gene expression comprising (I)

15. Document ID: AU 707349 B, WO 9605303 A1, AU 9532723 A, EP 777731 A1, US 5695993 A, US 5852171 A
L5: Entry 15 of 15

File: DWPI

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699

DERWENT-WEEK: 199938

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TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor binding, enhance inflammatory response

PRIORITY-DATA: 1994US-0289699 (August 12, 1994), 1997US-0878283 (June 18, 1997)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE
PAGES

MAIN-IPC

AU 707349 B	July 8, 1999	N/A	000	C12N015/12
WO 9605303 A1	February 22, 1996	E	058	C12N015/12
AU 9532723 A	March 7, 1996	N/A	000	C12N015/12
EP 777731 A1	June 11, 1997	E	000	C12N015/12
US 5695993 A	December 9, 1997	N/A	028	C12N005/16
US 5852171 A	December 22, 1998	N/A	000	C07K014/705

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

AU 707349B	August 9, 1995	1995AU-0032723	N/A	
AU 707349B		AU 9532723		Previous Publ.
AU 707349B		WO 9605303		Based on
WO 9605303A1	August 9, 1995	1995WO-US09636	N/A	
AU 9532723A	August 9, 1995	1995AU-0032723	N/A	
AU 9532723A		WO 9605303		Based on
EP 777731A1	August 9, 1995	1995EP-0929335	N/A	
EP 777731A1	August 9, 1995	1995WO-US09636	N/A	
EP 777731A1		WO 9605303		Based on

US 5695993A

August 12, 1994

1994US-0289699

N/A

US 5852171A

August 12, 1994

1994US-0289699

Div ex

US 5852171A

June 18, 1997

1997US-0878283

N/A

US 5852171A

US 5695993

Div ex

INT-CL (IPC): A61K 38/17; A61K 39/395; C07H 21/04; C07K 14/705;
C07K 16/28; C12N 5/16; C12N 15/11; C12N
15/12; G01N 33/68

IN: ESMON, C T, FUKUDOME, K

AB: Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new.

Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment

specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which

up-regulate its expression are useful to inhibit inflammatory responses (claimed). This

inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis,

septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter

its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with

blood will render the surfaces anticoagulant as EPCR binds and concentrates the

anticoagulant activated protein C at the surface. Its function can also be enhanced by

overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients

with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent

(activated) protein C binding to EPCR it is possible to enhance an inflammatory response and

so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor

(EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an

antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR

and substances which up-regulate its expression are useful to inhibit inflammatory responses

(claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke,

thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds.

which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in

contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the

anticoagulant activated protein C at the surface. Its function can also be enhanced by

overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients

with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent

(activated) protein C binding to EPCR it is possible to enhance an inflammatory response and

so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor

(EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an

antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR

and substances which up-regulate its expression are useful to inhibit

inflammatory responses

(claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke,

thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds.

which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in

contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the

anticoagulant activated protein C at the surface. Its function can also be enhanced by

overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients

with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent

(activated) protein C binding to EPCR it is possible to enhance an inflammatory response and

so treat solid tumours.

L5: Entry 15 of 15

File: DWPI

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699

DERWENT-WEEK: 199938

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TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit

inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor

binding, enhance inflammatory response

ABTX:

Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are:

(1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically

immunoreactive with a unique epitope of EPCR.

ABEQ:

Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are:

(1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically

immunoreactive with a unique epitope of EPCR.

ABEQ:

Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are:

(1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically

immunoreactive with a unique epitope of EPCR.

I. Document ID: US 6120989 A

L7: Entry 1 of 44

File: USPT

Sep 19, 2000

US-PAT-NO: 6120989

DOCUMENT-IDENTIFIER: US 6120989 A

TITLE: Isolated human cytomegalovirus polypeptides and uses thereof
DATE-ISSUED: September 19, 2000

US-CL-CURRENT: 435/5; 424/185.1, 424/192.1, 424/230.1, 435/69.1,
435/69.3, 435/7.92, 435/7.94,
435/975, 530/324, 530/328, 536/23.72, 930/220

APPL-NO: 8/ 506553

DATE FILED: July 25, 1995

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY

	APPL-NO	APPL-DATE
DE	44 26 453	July 26, 1994
DE	44 35 789	October 6, 1994

IN: Vornhagen; Rolf, Hinderer; Walter, Sonneborn; Hans-H.,
Plachter; Bodo, Jahn;
Gerhard

AB: Diagnostically relevant polypeptides and fusion proteins comprising an amino acid sequence which originates from cytomegalovirus and corresponds to a region of the major DNA-binding protein or of the C-terminal region of the tegument protein pp150 fused with at least one further fragment from another antigenic protein of cytomegalovirus are disclosed. The major DNA-binding protein is encoded by the reading frame UL57. The poly-peptides and fusion proteins according to the invention can be used in an advantageous manner in diagnostic tests and methods for the detection of IgM antibodies against cytomegalovirus.

L7: Entry 1 of 44
File: USPT
Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6120989 A
TITLE: Isolated human cytomegalovirus polypeptides and uses thereof

ABPL:
Diagnostically relevant polypeptides and fusion proteins comprising an amino acid sequence which originates from cytomegalovirus and corresponds to a region of the major DNA-binding protein or of the C-terminal region of the tegument protein pp150 fused with at least one further fragment from another antigenic protein of cytomegalovirus are disclosed. The major DNA-binding protein is encoded by the reading frame UL57. The poly-peptides and fusion proteins according to the invention can be used in an advantageous manner in diagnostic tests and methods for the detection of IgM antibodies against cytomegalovirus.

2. Document ID: US 5916874 A

L7: Entry 2 of 44
File: USPT
Jun 29, 1999

US-PAT-NO: 5916874
DOCUMENT-IDENTIFIER: US 5916874 A
TITLE: Method for treating liver injury
DATE-ISSUED: June 29, 1999

US-CL-CURRENT: 514/12; 530/350, 530/380, 530/381

APPL-NO: 8/ 733564
DATE FILED: October 18, 1996

PARENT-CASE:
This application is a continuation-in-part of PCT Application No. PCT/JP95/00704, filed on Apr. 10, 1995, which designated the United States and on which priority is claimed under 35 U.S.C. .sectn. 120.

FOREIGN-APPL-PRIORITY-DATA:	
COUNTRY	APPL-NO
JP	6-081196
	APPL-DATE
	April 20, 1994

IN: Fujiwara; Kenji, Mochida; Satoshi

AB: Disclosed is a method for treating liver injury caused by microorganism or toxic substance, which comprises administering to a patient suffering from liver injury a composition comprising a thrombomodulin, which has the ability to bind to thrombin and promote the activation of protein C by thrombin, as an active ingredient and at least one pharmaceutically acceptable carrier. The method of the present invention is very effective for ameliorating liver injury, such as fulminant hepatitis and hepatic veno-occlusive disease (VOD) which is likely to frequently occur after bone marrow transplantation.

L7: Entry 2 of 44
File: USPT
Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916874 A
TITLE: Method for treating liver injury

ABPL:
Disclosed is a method for treating liver injury caused by microorganism or toxic substance, which comprises administering to a patient suffering from liver injury a composition comprising a thrombomodulin, which has the ability to bind to thrombin and promote the activation of protein C by thrombin, as an active ingredient and at least one pharmaceutically acceptable carrier. The method of the present invention is very effective for ameliorating liver injury, such as fulminant hepatitis and hepatic veno-occlusive disease (VOD) which is likely to frequently occur after bone marrow transplantation.

CLPR:
1. A method for ameliorating liver injury due to fulminant hepatitis or hepatic veno-occlusive disease in a patient which comprises administering to a patient in need thereof an effective amount of thrombomodulin to suppress the serum level of glutamic pyruvic transaminase and bilirubin, wherein said thrombomodulin has the ability to bind to thrombin and promote the activation of protein C by thrombin, and wherein said thrombomodulin is soluble thrombomodulin which lacks a transmembrane domain or which is surfactant-treated thrombomodulin which contains a transmembrane domain.

3. Document ID: US 5852171 A

L7: Entry 3 of 44

File: USPT

Dec 22, 1998

US-PAT-NO: 5852171

DOCUMENT-IDENTIFIER: US 5852171 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DATE-ISSUED: December 22, 1998

US-CL-CURRENT: 530/350; 530/380

APPL-NO: 8/ 878283

DATE FILED: June 18, 1997

PARENT-CASE:

This is a divisional of U.S. Ser. No. 08/289,699, filed on Aug. 12, 1994, now U.S. Pat. No. 5,695,993.

IN: Fukudome; Kenji; Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in a Ca^{2+} dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L7: Entry 3 of 44

File: USPT

Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5852171 A

TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DEPR:

As described herein, a variety of compounds can be used to inhibit or enhance expression of the EPCR. The nature of the disorder will determine if the expression should be enhanced or inhibited. For example, based on the studies involving the use of an anti-protein C antibody in combination with cytokine, it should be possible to treat solid tumors by enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor by administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis, stroke, thrombosis, septic shock, adult respiratory distress syndrome, and pulmonary emboli using a method for inhibiting an inflammatory response involving administration

of EPCR or EPCR

fragments or substances that upregulate EPCR expression to a patient in need of treatment thereof.

4. Document ID: US 5830448 A

L7: Entry 4 of 44

File: USPT

Nov 3, 1998

US-PAT-NO: 5830448

DOCUMENT-IDENTIFIER: US 5830448 A

TITLE: Compositions and methods for the treatment of tumors

DATE-ISSUED: November 3, 1998

US-CL-CURRENT: 424/85.2; 424/85.1, 424/85.5, 514/2, 530/351, 530/381

APPL-NO: 8/ 470777

DATE FILED: June 6, 1995

PARENT-CASE:

This is a divisional of application Ser. No. 08/260,850 filed on 16 Jun. 1994, which application is incorporated herein by reference and to which application priority is claimed under 35 USC .sectn. 120.

IN: Vohar; Gordon A.

AB: The invention concerns a method for inhibiting the growth and/or causing regression of tumors by administering a therapeutically effective dose of a procoagulant and a cytokine, preferably TNF-.beta., TNF-.alpha. and/or IL-1. In a specific aspect, the invention concerns a method for tumor treatment by the administration of a therapeutically effective amount of a thrombomodulin inhibitor and a cytokine. The invention also concerns thrombomodulin inhibitors and pharmaceutical compositions used in the course of these treatments.

L7: Entry 4 of 44

File: USPT

Nov 3, 1998

DOCUMENT-IDENTIFIER: US 5830448 A

TITLE: Compositions and methods for the treatment of tumors

DEPR:

The treatment of the present invention may be combined with known tumor therapies, such as radiation therapy, chemotherapy, and immunotoxin therapy, including the administration of immunotoxin directed against the tumor vasculature as described by Burrows and Thorpe, supra. Most preferably, the treatment of the present invention is combined with the administration of a (further) inhibitor of the protein C system, which may, for example, be antibodies to protein C or activated protein, C, antibodies to protein S, inactivated protein C and C4b binding protein, as described in U.S. Pat. No. 5,147,638. In addition, steroids or other agents known to reduce or prevent platelet loss may be administered prior to, during or after

treatment.

5. Document ID: US 5827824 A

L7: Entry 5 of 44

File: USPT

Oct 27, 1998

US-PAT-NO: 5827824
DOCUMENT-IDENTIFIER: US 5827824 A
TITLE: Protease-resistant thrombomodulin analogs
DATE-ISSUED: October 27, 1998

US-CL-CURRENT: 514/12, 514/822, 530/380, 530/402, 530/412, 530/419

APPL-NO: 8/ 463605
DATE FILED: June 5, 1995

PARENT-CASE:

This application is a division of U.S. application Ser. No. 08/197,576, filed Feb. 16, 1994, which is a continuation of U.S. application Ser. No. 07/830,577, filed Feb. 5, 1992, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/568,456, filed Aug. 15, 1990 abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/506,325, filed Apr. 9, 1990, now U.S. Pat. No. 5,256,770, which is a continuation-in-part of U.S. application Ser. No. 07/406,941, filed Sep. 13, 1989, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/345,372, filed Apr. 28, 1989, now abandoned, all of whose disclosures are entirely incorporated by reference herein. This application also claims foreign priority from the PCT application Ser. No. 90/00955, filed Feb. 16, 1990, which became U.S. application Ser. No. 07/730,975, filed Jul. 29, 1991, now abandoned, which claims priority from U.S. application Ser. No. 07/406,941, filed Sep. 13, 1989 abandoned, which was a continuation-in-part of U.S. application Ser. No. 07/345,372, filed Apr. 28, 1989, now abandoned, which was a continuation-in-part of U.S. application Ser. No. 07/312,141, filed Feb. 17, 1989, now abandoned.

IN: Light: David Richard, Andrews; William H., Clarke; Jeffrey Homer, Wydro; Robert Michael, Young; Patricia Ann

AB: The present invention relates to the single-chain thrombomodulin ("TM") and analogs thereof that are not susceptible to cleavage by proteases and retain the biological activity of thrombomodulin, as well as methods of use in, for example, antithrombotic therapy. Novel proteins, nucleic acid gene sequences, pharmaceuticals and methods of inhibiting thrombotic activity are disclosed.

L7: Entry 5 of 44

File: USPT

Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827824 A
TITLE: Protease-resistant thrombomodulin analogs

CLPR:

2. A method of treating thrombotic disease, comprising administering an effective amount of a thrombomodulin protein analog, wherein the amino acid sequence of the N-terminus is modified by substitution or deletion of one or more amino acids at the N-terminus to prevent signal sequence cleavage heterogeneity, whereby the analog has a single N-terminus, and wherein the analog has at least 50% of the ability to potentiate thrombin-mediated activation of protein C as said protein having a native thrombomodulin N-terminus wherein said analog comprises a polypeptide having an amino acid sequence corresponding to the lectin binding, EGF and O-linked glycosylation domains of native thrombomodulin.

6. Document ID: US 5762921 A

L7: Entry 6 of 44

File: USPT

Jun 9, 1998

US-PAT-NO: 5762921
DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors
DATE-ISSUED: June 9, 1998

US-CL-CURRENT: 424/85.1; 424/158.1, 424/198.1, 424/85.2, 424/85.5, 514/12, 530/350, 530/351, 530/381

APPL-NO: 8/ 594360
DATE FILED: January 30, 1996

PARENT-CASE:

This is a continuation of application Ser. No. 08/260,850 filed on 16 Jun. 1994 (now abandoned), which application(s) is(are) incorporated herein by reference and to which application(s) priority is claimed under 35 USC .sectn. 120.

IN: Vehar; Gordon A.

AB: The invention concerns a method for inducing a selective collapse of the vasculature of a solid tumor by administering to a patient a therapeutically effective dose of a combination of a compound preventing the formation of a functional thrombin-thrombomodulin complex and a cytokine selected from the group of TNF- β , (LT), TNF- α , IL-1, and IFN- γ . The invention further concerns the composition used in this method.

L7: Entry 6 of 44

File: USPT

Jun 9, 1998

DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors

DEPR:

The treatment of the present invention may be combined with known tumor therapies, such as radiation therapy, chemotherapy, and immunotoxin therapy, including the

administration of
immunotoxin directed against the tumor vasculature as described by
Burrows and Thorpe, supra.
Most preferably, the treatment of the present invention is combined with
the administration of a
(further) inhibitor of the protein C system which may, for example, be
antibodies to protein C or
activated protein, C, antibodies to protein S, inactivated protein C and C4b
binding protein, as
described in U.S. Pat. No. 5,147,638. In addition, steroids or other agents
known to reduce or
prevent platelet loss may be administered prior to, during or after
treatment.

7. Document ID: US 5695993 A

L7: Entry 7 of 44

File: USPT

Dec 9, 1997

US-PAT-NO: 5695993
DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated
protein C receptor
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/325; 435/320.1, 435/69.1, 536/23.5

APPL-NO: 8/ 289699
DATE FILED: August 12, 1994

IN: Fukudome, Kenji, Esmon, Charles T.

AB: Human protein C and activated protein C were shown to bind to
endothelium
specifically, selectively and saturably ($K_d=30$ nM, 7000 sites per cell) in
a Ca²⁺-dependent fashion. Expression cloning revealed a 1.3 kb CDNA that
coded for a novel type I
transmembrane glycoprotein capable of binding protein C. This protein
appears to be a member
of the CD1/MHC superfamily. Like thrombomodulin, the receptor
involved in protein C
activation, the endothelial cell protein C receptor (EPCR) function and
message are both
down regulated by exposure of endothelium to TNF. Identification of
EPCR as a member of the
CD1/MHC superfamily provides insights into the role of protein C in
regulating the
inflammatory response, and determination of methods for pharmaceutical
use in manipulating
the inflammatory response.

L7: Entry 7 of 44

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated
protein C receptor

DEPR:
As described herein, a variety of compounds can be used to inhibit or
enhance expression of the
EPCR. The nature of the disorder will determine if the expression should
be enhanced or
inhibited. For example, based on the studies involving the use of an

anti-protein C antibody in
combination with cytokine, it should be possible to treat solid tumors by
enhancing an
inflammatory response involving blocking of protein C or activated protein
C binding to an
endothelial cell protein C/activated protein C receptor by administering to a
patient in need of
treatment thereof an amount of a compound blocking binding of protein C
or activated protein C to
the receptor. Similarly, it should be possible to treat disorders such as gram
negative sepsis,
stroke, thrombosis, septic shock, adult respiratory distress syndrome, and
pulmonary emboli using
a method for inhibiting an inflammatory response involving administration
of EPCR or EPCR
fragments or substances that upregulate EPCR expression to a patient in
need of treatment thereof.

8. Document ID: US 5695964 A

L7: Entry 8 of 44

File: USPT

Dec 9, 1997

US-PAT-NO: 5695964
DOCUMENT-IDENTIFIER: US 5695964 A
TITLE: Recombinant DNA vectors, including plasmids, and host cells for
production of truncated
thrombomodulin
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/69.6; 435/243, 435/320.1, 435/325, 435/358

APPL-NO: 8/ 587389
DATE FILED: January 17, 1996

PARENT-CASE:
This is a Division of application Ser. No. 08/307,444 filed Sep. 19, 1994,
now issued as U.S.
Pat. No. 5,516,659, which in turn is a Continuation of application Ser. No.
07/835,436 filed Mar.
27, 1992, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY

	APPL-NO	APPL-DATE
JP	Hei 2-168766	June 27, 1990

IN: Nii, Atsushi, Morishita, Hideaki, Uemura, Akio, Mochida, Ei

AB: This invention relates to novel vectors and host cells containing
nucleic acids
coding for a polypeptide having thrombin binding ability, anticoagulant
activity and
thrombolytic activity. The polypeptide can be efficiently produced in
large quantities by
means of genetic recombination techniques using the vectors and host
cells of the present
invention. Since the polypeptide exhibits anticoagulant activity and
thrombolytic activity
without generating side effects such as bleeding tendencies, it can be
applied effectively
to the prevention and treatment of hypercoagulability-related diseases.

L7: Entry 8 of 44

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695964 A

TITLE: Recombinant DNA vectors, including plasmids, and host cells for production of truncated thrombomodulin

DEPR:

The polypeptide of the present invention imparts an effect of inhibiting both blood coagulation and platelet aggregation because of its function to bind to thrombin and inactivate the activity thereof and, at the same time, exhibits anticoagulant and thrombolytic activities by activating protein C. Because of such effects, it is possible to use the polypeptide for the treatment of a broad range of hypercoagulability-related diseases, based on its thrombus formation inhibiting activity, thrombolytic activity, anti-DIC activity and the like. Especially, reduction of side effects can be expected because of its excellent function to activate protein C.

9. Document ID: US 5545721 A

L7: Entry 9 of 44

File: USPT

Aug 13, 1996

US-PAT-NO: 5545721

DOCUMENT-IDENTIFIER: US 5545721 A

TITLE: Conjugates for the prevention and treatment of sepsis

DATE-ISSUED: August 13, 1996

US-CL-CURRENT: 530/391.7, 530/300, 530/317, 530/319, 530/322, 530/345, 530/350, 530/391.1, 530/391.5, 530/391.9, 530/402

APPL-NO: 8/ 169701

DATE FILED: December 17, 1993

PARENT-CASE:

RELATED APPLICATION DATA This Application is a Continuation-in-Part Application of application Ser. No. 07/995,388, filed on Dec. 21, 1992, now abandoned.

IN: Carroll; Sean B., Firca; Joseph R., Pugh; Charles, Padhye; Nisha V.

AB: Compositions and methods are described for preventing and treating sepsis in humans and other animals. Surgical patients, low birth weight infants, burn and trauma victims, as well as other individuals at risk can be treated prophylactically. Methods for treating acute infections with advantages over current therapeutic approaches are provided.

Conjugates and methods of making conjugates for the prevention and treatment of sepsis are described.

L7: Entry 9 of 44

File: USPT

Aug 13, 1996

DOCUMENT-IDENTIFIER: US 5545721 A

TITLE: Conjugates for the prevention and treatment of sepsis

BSPR:

The present invention contemplates a method of treatment, comprising: (a) providing a mammal for treatment; (b) providing a therapeutic preparation, comprising an endotoxin-binding compound covalently bound to protein; and (c) administering the preparation to the mammal (e.g., intravenous). The endotoxin-binding compound may be polymyxin and the protein is preferably non-specific immunoglobulin such as IgG.

10. Document ID: US 5516659 A

L7: Entry 10 of 44

File: USPT

May 14, 1996

US-PAT-NO: 5516659

DOCUMENT-IDENTIFIER: US 5516659 A

TITLE: Truncated thrombomodulin, recombinant production thereof, and therapeutic agent

DATE-ISSUED: May 14, 1996

US-CL-CURRENT: 435/69.6; 514/2, 514/8, 530/350, 530/395, 536/23.5

APPL-NO: 8/ 307444

DATE FILED: September 19, 1994

PARENT-CASE:

This is a continuation of application Ser. No. 07/835,436 filed Mar. 27, 1992, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

APPL-NO

APPL-DATE

JP

2-168766

June 27, 1990

IN: Nii; Atsushi, Morishita; Hideaki, Uemura; Akio, Mochida; Ei

AB: This invention relates to a novel polypeptide which is obtained by means of genetic recombination DNA techniques and has thrombin binding ability, anticoagulant activity and thrombolytic activity. The polypeptide of the present invention can be produced in a large quantity and efficiently by means of genetic recombination techniques. Since the polypeptide of the present invention exhibits anticoagulant activity and thrombolytic activity without generating side effects such as bleeding tendency, it can be applied effectively to the prevention and treatment of hypercoagulability-related diseases.

L7: Entry 10 of 44

File: USPT

May 14, 1996

DOCUMENT-IDENTIFIER: US 5516659 A

TITLE: Truncated thrombomodulin, recombinant production thereof, and

therapeutic agent

DEPR:

The polypeptide of the present invention imparts an effect of inhibiting both blood coagulation and platelet aggregation because of its function to bind to thrombin and inactivate the activity thereof and, at the same time, exhibits anticoagulant and thrombolytic activities by activating protein C. Because of such effects, it is possible to use the polypeptide for the treatment of a broad range of hypercoagulability-related diseases, based on its thrombus formation inhibiting activity, thrombolytic activity, anti-DIC activity and the like. Especially, reduction of side effects can be expected because of its excellent function to activate protein C.

11. Document ID: US 5254532 A

L7: Entry 11 of 44

File: USPT

Oct 19, 1993

US-PAT-NO: 5254532

DOCUMENT-IDENTIFIER: US 5254532 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same
DATE-ISSUED: October 19, 1993

US-CL-CURRENT: 514/2; 514/12, 514/21, 514/8

DISCLAIMER DATE: 20090901

APPL-NO: 7/ 840719

DATE FILED: February 21, 1992

PARENT-CASE:

This application is a continuation of application Ser. No. 07/540,357, filed on Jun. 19, 1990, now U.S. Pat. No. 5,143,901.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

AT	APPL-NO	APPL-DATE
	1551/89	June 26, 1989

IN: Schwarz; Hans P., Molinari; Ewald, Linnau; Yendra, Pfeiler; Susanne

AB: A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

L7: Entry 11 of 44

File: USPT

Oct 19, 1993

DOCUMENT-IDENTIFIER: US 5254532 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same

ABPL:

A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

BSPR:

To obtain this object, the invention provides preparation for treating and preventing thromboses and thromboembolic complications, having a protein S content in a concentration that is at least 50 times that of native plasma and being free from C4b-binding protein optionally in combination with a content of activates protein C.

12. Document ID: US H001148 H

L7: Entry 12 of 44

File: USPT

Mar 2, 1993

US-PAT-NO: H001148

DOCUMENT-IDENTIFIER: US H001148 H

TITLE: Method of separating activated human protein C
DATE-ISSUED: March 2, 1993

US-CL-CURRENT: 435/13; 435/219, 435/815, 436/548

APPL-NO: 7/ 815870

DATE FILED: January 3, 1992

PARENT-CASE:

This application is a continuation of now abandoned application Ser. No. 07/181,424, filed on Apr. 14, 1988.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

JP	APPL-NO	APPL-DATE
	62-93377	April 17, 1987

IN: Wakabayashi; Kenji, Sumi; Yoshihiko, Ichikawa; Yataro, Sakata; Yoichi, Aoki; Nobuo

AB: A method of separating activated human protein C, which comprises bringing a mixture containing activated human protein C having a gamma-carboxyglutamic acid (Gla) domain in the presence of a calcium ion into contact with a fixed antibody comprising an insoluble carrier and fixed thereto an antibody to a complex of human protein C and a calcium ion bound to the Gla domain whereby the activated human protein C is captured by the fixed antibody in the form in which the calcium ion is bound to the Gla domain. A method is also provided for separating activated human protein C from a mixture

containing human protein C and activated human protein C, which comprises bringing a first mixture containing human protein C and activated human protein C having a Gla domain into contact with a first fixed antibody comprising an insoluble carrier and fixed thereto a first antibody to human protein C but not to activated human protein C to form a second mixture substantially free from human protein C while the human protein C is captured by the first fixed antibody, and bringing the second mixture in the presence of a calcium ion into contact with a second fixed antibody comprising an insoluble carrier and fixed thereto a second antibody to a complex of human protein C and a calcium ion bound at the Gla domain, whereby the activated human protein C is captured by the second fixed antibody in the form in which the calcium ion is bound to the Gla domain.

L7: Entry 12 of 44

File: USPT

Mar 2, 1993

DOCUMENT-IDENTIFIER: US H001148 H

TITLE: Method of separating activated human protein C

CLPR:

1. A method of separating activated human protein C, which has a gamma-carboxyglutamic acid (Gla) domain and is biologically active, from a mixture containing activated human protein C, which comprises bringing a mixture containing activated human protein C having a Gla domain in the presence of calcium into contact with a fixed monoclonal antibody comprising an insoluble carrier and fixed thereto a monoclonal antibody specific to a human protein C having a calcium ion bound to the Gla domain, whereby the activated human protein C having a calcium ion bound to the Gla domain is bound to the fixed monoclonal antibody, and then treating the fixed monoclonal antibody binding the activated human protein C having the calcium ion bound to its Gla domain with an aqueous medium substantially free from calcium ions, whereby the activated human protein C is released from the fixed antibody in a form not binding the calcium ion in the Gla domain.

CLPV:

(2) bringing the second mixture in the presence of calcium into contact with a second fixed monoclonal antibody comprising an insoluble carrier and fixed thereto a second antibody specific to human protein C having a calcium ion bound to the Gla domain, whereby the activated human protein C having a calcium ion bound to the Gla domain is bound to the second fixed monoclonal antibody, and then treating the second monoclonal antibody, and then treating the second monoclonal antibody capturing the activated human protein C having the calcium ion bound to its Gla domain with an aqueous medium substantially free from calcium ions, whereby the activated human protein C is separated from the second fixed antibody in a form not binding the calcium ion in the Gla domain.

13. Document ID: US 5143901 A

L7: Entry 13 of 44

File: USPT

Sep 1, 1992

US-PAT-NO: 5143901

DOCUMENT-IDENTIFIER: US 5143901 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same
DATE-ISSUED: September 1, 1992

US-CL-CURRENT: 514/2; 514/12, 514/21, 514/8

APPL-NO: 7/ 540357

DATE FILED: June 19, 1990

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

APPL-NO

APPL-DATE

AT

1551/89

June 26, 1989

IN: Schwarz; Hans P., Molinari; Ewald, Linnau; Yendra, Pfeiler; Susanne

AB: A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

L7: Entry 13 of 44

File: USPT

Sep 1, 1992

DOCUMENT-IDENTIFIER: US 5143901 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same

ABPL:

A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

BSPR:

To obtain this object, the invention provides a preparation for treating and preventing thromboses and thromboembolic complications, having a protein S content in a concentration that is at least 50 times that of native plasma and being free from C4b-binding protein, optionally in combination with a content of activated protein C.

14. Document ID: US 4849403 A

L7: Entry 14 of 44

File: USPT

Jul 18, 1989

US-PAT-NO: 4849403

DOCUMENT-IDENTIFIER: US 4849403 A

TITLE: Protein C activator, methods of preparation and use thereof

DATE-ISSUED: July 18, 1989

US-CL-CURRENT: 512/2; 424/542, 435/23, 435/24, 435/68.1, 530/381

APPL-NO: 6/ 861786

DATE FILED: May 9, 1986

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY

	APPL-NO	APPL-DATE
CH	2267/85	May 29, 1985
CH	4135/84	September 25, 1985
CH	5087/85	November 28, 1985

IN: Stocker; Kurt F., Svendsen; Lars G.

AB: A method and composition for assaying protein C is described. The method comprises reacting a protein C-containing medium with a protein C-activating activator preparation obtained from venom of the snake Agkistrodon contortrix, or venom of another snake species which undergoes an immunological cross-reaction with the venom of Agkistrodon contortrix, to cause maximum activation of protein C and subsequently determining the quantity of activated protein C, said quantity being proportional to the amount of protein C in said medium. Also disclosed is a method and composition for treating thrombotic disorders with the activator preparation and a method of obtaining the activator preparation by culturing of a cloned microorganism.

L7: Entry 14 of 44

File: USPT

Jul 18, 1989

DOCUMENT-IDENTIFIER: US 4849403 A

TITLE: Protein C activator, methods of preparation and use thereof

BSPR:

The activator preparation of the invention may also be obtained by dilution of the snake venom in an aqueous medium, removal of the undesired venom components from the solution either by fractionated alcohol precipitation, fractionated salt precipitation or heat treatment at an acid pH for the purpose of preparing a pre-purified venom fraction, further purification of the obtained pre-purified venom fraction by chromatography on an anion exchanger having the appropriate porosity for binding proteins, e.g. cross-linked diethylaminoethyl-dextran or diethylaminoethyl-cellulose, elution with sodium phosphate buffer at neutral pH and increasing ionic strength, further chromatography on a cation exchanger, e.g. cross-linked carboxymethyl-dextran or carboxymethyl-cellulose, elution with a sodium

acetate buffer at an acid

pH, concentration of the protein C-activating eluates by ultrafiltration, removal of electrolytes

and final purification of the concentrate by chromatography on a molecular sieve gel, e.g. a cross-linked dextran gel, using diluted aqueous acetic acid as the eluent, and subsequent lyophilization.

BSPR:

Fresh, frozen or lyophilized blood plasma from men or mammals comprising the usual calcium ion-binding additives, such as citrate or oxalate, or plasma preparations from which inhibitors or components irrelevant to the protein C assay were removed by heating, pH adjustment or treatment with enzymes, adsorbing or protein-precipitating agents, can be used as natural substrates for measuring the action of activated protein C via inactivation of factors V and VIII in the clotting test. In addition, clotting factor concentrates from blood plasma or by-products thereof, which are applied for therapeutical purposes, and factor-deficient plasma can be used as well.

15. Document ID: US 4638050 A

L7: Entry 15 of 44

File: USPT

Jan 20, 1987

US-PAT-NO: 4638050

DOCUMENT-IDENTIFIER: US 4638050 A

TITLE: Thrombin-binding substance and process for its production

DATE-ISSUED: January 20, 1987

US-CL-CURRENT: 530/413; 424/583, 530/350, 530/399, 530/851

APPL-NO: 6/ 713821

DATE FILED: March 20, 1985

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY

	APPL-NO	APPL-DATE
JP	59-55792	March 23, 1984

IN: Aoki; Nobuo, Kurosawa; Shinichiro

AB: A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000.+-.20,000 in reduced condition and 71,000.+-.20,000 in unreduced condition; (b) isoelectric point: .sub.p H 4.2.+-.0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a .sub.p H range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

L7: Entry 15 of 44

File: USPT

Jan 20, 1987

DOCUMENT-IDENTIFIER: US 4638050 A

TITLE: Thrombin-binding substance and process for its production

ABPL:

A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000 +/- 20,000 in reduced condition and 71,000 +/- 20,000 in unreduced condition; (b) isoelectric point: .sub.p H 4.2 +/- 0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a .sub.p H range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

16. Document ID: US 4259357 A

L7: Entry 16 of 44

File: USPT

Mar 31, 1981

US-PAT-NO: 4259357

DOCUMENT-IDENTIFIER: US 4259357 A

TITLE: Stabilized milkproteins-containing compositions

DATE-ISSUED: March 31, 1981

US-CL-CURRENT: 426/42; 426/56, 426/623, 426/63, 426/630, 426/634, 426/635, 426/641, 426/807

APPL-NO: 6/ 043512

DATE FILED: May 29, 1979

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

APPL-NO

APPL-DATE

GB

25165/78

May 31, 1978

IN: Van Kranenburg; Simon

AB: A process for stabilizing an aqueous composition, which contains insoluble components mainly consisting of insoluble protein, insoluble carbohydrates and fats, which tend either to precipitate or to migrate to the surface of the composition, which process comprises incorporating into a dry composition a stabilizing proportion of a casein which has been enzymatically hydrolysed under conditions such that the K-casein moiety has been hydrolysed whereas no peptides having a molecular weight below 10.sup.4 have been formed.

L7: Entry 16 of 44

File: USPT

Mar 31, 1981

DOCUMENT-IDENTIFIER: US 4259357 A

TITLE: Stabilized milkproteins-containing compositions

CLPR:

1. A process for producing a dry composition, which on dilution with water yields a homogenous aqueous composition, said process for producing said dry composition comprising: admixing (a) from 10 to 30 wt. % fat, (b) from 10 to 30 wt % protein, (c) from 10 to 50 wt. % carbohydrates said composition having at least part of the protein and the carbohydrates water-insoluble, (d) at least 0.5 wt. % of a casein stabilizer which has been treated with an effective amount of a proteolytic enzyme under conditions such that the K-casein moiety contained in said casein is hydrolysed without forming peptides having a molecular weight of below 10.sup.4 and (e) from 0.1 to 10 wt. %, based on the amount of protein, of a water-soluble or water-dispersible salt which binds calcium and magnesium ions.

CLPR:

20. A dry composition, which upon dilution with water yields a homogeneous aqueous animal feed composition, said dry composition comprising (a) from 10 to 30 wt. % fat, (b) from 10 to 30 wt. % protein, (c) from 10 to 50 wt. % carbohydrates said composition having at least part of the protein and the carbohydrates water-insoluble, (d) at least 0.5 wt. % of a casein stabilizer which has been treated with an effective amount of a proteolytic enzyme under conditions such that the K-casein moiety contained in said casein is hydrolysed without forming peptides having a molecular weight below 10.sup.4, or at least 0.5 wt. % of untreated casein containing K-casein and an effective amount of a proteolytic enzyme selected from the group consisting of rennet and rennet substitutes, and (e) from 0.1 to 10 wt. %, based on the amount of protein, of a water-soluble or water-dispersible salt which binds calcium and magnesium ions.

17. Document ID: JP 08291193 A

L7: Entry 17 of 44

File: JPAB

Nov 5, 1996

PUB-NO: JP408291193A

DOCUMENT-IDENTIFIER: JP 08291193 A

TITLE: MEDICINAL COMPOSITION CONTAINING PEPTIDE HAVING ACTION PROMOTING ACTIVATION OF PROTEIN C BY THROMBIN

PUBN-DATE: November 5, 1996

INT-CL (IPC): C07H 21/04; A61K 38/00; C12N 15/09; C12P 21/02

APPL-NO: JP08138587

APPL-DATE: May 31, 1996

IN: YAMAMOTO, SHUJI, SUZUKI, KOJI

AB: PURPOSE: To obtain a medicinal composition for treating circulatory diseases, etc., by blending a peptide capable of promoting activation of a protein C

by thrombin and
having action of antiblood coagulation, suppression of platelet
agglutination, thrombolysis,
etc., with an administrable carrier for medicines., CONSTITUTION: This
medicine composition
for controlling blood coagulation and platelet agglutination is obtained by
blending a
peptide having action binding to thrombin and promoting activation of
protein C by thrombin
and having a partial arrangement of amino acid sequence capable of
coding DNA derived from
human and having a restriction enzyme site expressed by a restriction
enzyme map of the
formula and having all of antiblood coagulation action, platelet
agglutination suppression
action and thrombolytic action, almost free from adverse effect and useful
as a treating
medicine for circulatory diseases, etc., with one or more kinds of carriers
among
saccharide, purified gelatin, albumin, mannitol, glucose and sodium
chloride which are
administrable as medicines and preparing the blend., COPYRIGHT:
(C)1996,JPO

L7: Entry 17 of 44

File: JPAB

Nov 5, 1996

DOCUMENT-IDENTIFIER: JP 08291193 A
TITLE: MEDICINAL COMPOSITION CONTAINING PEPTIDE
HAVING ACTION PROMOTING ACTIVATION OF PROTEIN C
BY THROMBIN

FPAR:

CONSTITUTION: This medicine composition for controlling blood
coagulation and platelet
agglutination is obtained by blending a peptide having action binding to
thrombin and promoting
activation of protein C by thrombin and having a partial arrangement of
amino acid sequence
capable of coding DNA derived from human and having a restriction
enzyme site expressed by a
restriction enzyme map of the formula and having all of antiblood
coagulation action, platelet
agglutination suppression action and thrombolytic action, almost free from
adverse effect and
useful as a treating medicine for circulatory diseases, etc., with one or
more kinds of carriers
among saccharide, purified gelatin, albumin, mannitol, glucose and sodium
chloride which are
administrable as medicines and preparing the blend.

18. Document ID: JP 08027200 A

L7: Entry 18 of 44

File: JPAB

Jan 30, 1996

PUB-NO: JP408027200A
DOCUMENT-IDENTIFIER: JP 08027200 A
TITLE: FUSED PROTEIN

PUBN-DATE: January 30, 1996

INT-CL (IPC): C07K 19/00; C07K 14/435; C12N 9/02; C12N 15/09;
C12P 21/02; C12Q 1/66; G01N 33/53;
G01N 33/535; C12Q 1/68

APPL-NO: JP06165223

APPL-DATE: July 18, 1994

IN: SUZUKI, EIJI, UEDA, HIROSHI, KAZAMI, JUN, KONO,
HAJIME

AB: PURPOSE: To obtain a fused protein capable of being simply
mixed with IgG to
label the IgG and useful as a labeled enzyme used for luminescent
immunoassay methods, etc.,
by binding a peptide containing an IgG-recognizing region to the end of
Cypridina luciferase
by a genetic engineering method., CONSTITUTION: The new fused
protein capable of being
simply mixed with IgG to label the IgG with Cypridina luciferase without
requiring a
chemical treatment for the labeling and useful as a labeling enzyme for
luminescent
immunoassay methods is obtained by binding a peptide containing a
region recognizing the IgG
Fc part of a protein A originated from Staphylococcus aureus, a peptide
containing a region
recognizing the IgG Fc part of a protein C originated from a
streptococcus, etc., to the
amino end of the Cypridina luciferase. The fused protein is obtained by
expressing a vector
which is produced by binding the gene of a peptide having a region
recognizing the IgG to
the 5'-site of Cypridina luciferase gene through a linker., COPYRIGHT:
(C)1996,JPO

L7: Entry 18 of 44

File: JPAB

Jan 30, 1996

DOCUMENT-IDENTIFIER: JP 08027200 A
TITLE: FUSED PROTEIN

FPAR:

CONSTITUTION: The new fused protein capable of being simply mixed
with IgG to label the IgG with
Cypridina luciferase without requiring a chemical treatment for the labeling
and useful as a
labeling enzyme for luminescent immunoassay methods is obtained by
binding a peptide containing a
region recognizing the IgG Fc part of a protein A originated from
Staphylococcus aureus, a
peptide containing a region recognizing the IgG Fc part of a protein C
originated from a
streptococcus, etc., to the amino end of the Cypridina luciferase. The fused
protein is obtained
by expressing a vector which is produced by binding the gene of a peptide
having a region
recognizing the IgG to the 5'-site of Cypridina luciferase gene through a
linker.

19. Document ID: WO 9534652 A1

L7: Entry 19 of 44

File: EPAB

Dec 21, 1995

PUB-NO: WO009534652A1
DOCUMENT-IDENTIFIER: WO 9534652 A1
TITLE: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST
PROTEIN C

PUBN-DATE: December 21, 1995

INT-CL (IPC): C12N 15/13; C07K 16/40; C07K 16/46; C07K 17/00;
A61K 39/395; A61K 33/06; A61K 38/19

EUR-CL (EPC): C07K016/40

APPL-NO: US09507372

APPL-DATE: June 9, 1995

PRIORITY-DATA:

IN: REZAIE, ALIREZA, ESMON, CHARLES T

AB: A Ca²⁺ dependent recombinant antibody that specifically binds to a specific twelve peptide sequence (E D Q V D P R L I D G K) in the activation region of the Protein C has been constructed. The antibody does not bind to Activated Protein C and can be used to inhibit activation of Protein C by thrombin-thrombomodulin, in purification of Protein C, and in treatment of tumors.

L7: Entry 19 of 44

File: EPAB

Dec 21, 1995

DOCUMENT-IDENTIFIER: WO 9534652 A1
TITLE: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

FPAR:

A Ca²⁺ dependent recombinant antibody that specifically binds to a specific twelve peptide sequence (E D Q V D P R L I D G K) in the activation region of the Protein C has been constructed. The antibody does not bind to Activated Protein C and can be used to inhibit activation of Protein C by thrombin-thrombomodulin, in purification of Protein C, and in treatment of tumors.

20. Document ID: US 5254532 A

L7: Entry 20 of 44

File: EPAB

Oct 19, 1993

PUB-NO: US005254532A

DOCUMENT-IDENTIFIER: US 5254532 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same

PUBN-DATE: October 19, 1993

INT-CL (IPC): A61K 37/00

EUR-CL (EPC): C07K014/745; C07K016/36, C07K016/40, C12N009/64

APPL-NO: US84071992

APPL-DATE: February 21, 1992

PRIORITY-DATA:

IN: SCHWARZ, HANS P, MOLINARI, EWALD, LINNAU,

YENDRA, PFEILER, SUSANNE

AB: A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

L7: Entry 20 of 44

File: EPAB

Oct 19, 1993

DOCUMENT-IDENTIFIER: US 5254532 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use of such a preparation and a method of producing the same

FPAR:

A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

21. Document ID: US 5143901 A

L7: Entry 21 of 44

File: EPAB

Sep 1, 1992

PUB-NO: US005143901A

DOCUMENT-IDENTIFIER: US 5143901 A

TITLE: TITLE DATA NOT AVAILABLE

PUBN-DATE: September 1, 1992

INT-CL (IPC): A61K 37/00

EUR-CL (EPC): C07K014/745; C07K016/36, C07K016/40, C12N009/64

APPL-NO: US54035790

APPL-DATE: June 19, 1990

PRIORITY-DATA:

IN: SCHWARZ, HANS P, MOLINARI, EWALD, LINNAU,
YENDRA, PFEILER, SUSANNE

AB: A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

L7: Entry 21 of 44

File: EPAB

Sep 1, 1992

DOCUMENT-IDENTIFIER: US 5143901 A
TITLE: TITLE DATA NOT AVAILABLE

FPAR:

A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

22. Document ID: US 4638050 A

L7: Entry 22 of 44

File: EPAB

Jan 20, 1987

PUB-NO: US004638050A
DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production

PUBN-DATE: January 20, 1987

INT-CL (IPC): C07K 14/745
EUR-CL (EPC): C07K014/745

APPL-NO: US71382185
APPL-DATE: March 20, 1985

PRIORITY-DATA:

IN: AOKI, NOBUO, KUROSAWA, SHINICHIRO

AB: A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000+/-20,000 in reduced condition and 71,000+/-20,000 in unreduced condition; (b) isoelectric point: pH 4.2+/-0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a pH range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

L7: Entry 22 of 44

File: EPAB

Jan 20, 1987

DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production

FPAR:

A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000+/-20,000 in reduced condition and 71,000+/-20,000 in unreduced condition; (b) isoelectric point: pH 4.2+/-0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a pH range of 2 to 10 and stable

to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

23. Document ID: WO 200066754 A1
L7: Entry 23 of 44

File: DWPI

Nov 9, 2000

DERWENT-ACC-NO: 2001-007227
DERWENT-WEEK: 200101
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TITLE: Protein C derivatives, useful for treating vascular occlusive disorder, hypercoagulable state, thrombotic disorder and disease states predisposing thrombosis, comprises specific amino acid substitutions

PRIORITY-DATA: 1999US-0131801 (April 30, 1999)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

WO 200066754 A1

November 9, 2000

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057

C12N015/57

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

WO 200066754A1

April 13, 2000

2000WO-US08722

N/A

INT-CL (IPC): A61K 38/48; C12N 5/10; C12N 9/64; C12N 15/57

IN: GERLITZ, B E, JONES, B E

AB: NOVELTY - A protein C derivative (I) comprising a fully defined sequence of 419 amino acids or corresponding to a fully defined sequence of 461 amino acids, where amino acid at position 194, 195, 228, 249, 254, 302 or 316 is substituted by S, A, T, H, K, R, N, D, E, G or Q, such that amino acid at position 195 is not substituted with A and amino acid at position 254 is not substituted with T, is new., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:, (1) a recombinant DNA molecule (II) encoding a protein C derivative in which L at position 194 is replaced with S or A and T at position 254 is replaced with S, and comprising a fully defined sequence of 1386 nucleotides:, (2) a pharmaceutical composition (PC) comprising a protein C derivative with increased resistance to serpins selected from L194S, L194S:T254S, or L194A:T254S:, (3) a vector (III) comprising (II):, (4) a host cell (IV) transformed with (III):, (5) an isolated nucleic

acid comprising
a protein C polynucleotide encoding at least 90% of amino acids of a fully defined sequence
(S1) comprising 419 amino acids; (6) a protein C derivative comprising at least 90% of amino acids of S1; (7) an article of manufacture for human pharmaceutical use, comprising a packaging material, and a vial comprising lyophilized (1); (8) preparing (1); and, (9)
treating thrombotic and vascular occlusive disorders or, hypercoagulable states by
inhibiting binding of activated protein C polypeptides to inhibitor recognition sequences of
serpins, PCI and alpha -I-AT.; ACTIVITY - Antibacterial; immunosuppressive; anticoagulant;
hemostatic; dermatological; tranquilizer; vulnerary; antiinflammatory; thrombolytic;
antisickling; antianemic; antiviral; cardiant; antianginal; cerebroprotective.; MECHANISM OF
ACTION - Regulator of homeostasis by inactivating factors Va, and VIIIa in the coagulation
cascade; amidolytic.; Amidolytic activity of recombinant human aPC polypeptides were
determined by hydrolysis of the tri-peptide chromogenic substrate S-2366 (Glu-Pro-Arg-p-nitroanilide). The anticoagulant activity was shown as measured clotting time
in an aPTT in 500 ng ml aPC. Reactions were performed in a 96-well micro l plate, and
amidolytic activity was measured as a change in absorbance units/minute at 405 nm.
Anti-coagulant activity was assessed by measuring the prolongation of clotting time in the
activated partial thromboplastin time clotting assay. Reactions were monitored in a
ThermoMax kinetic microtiter plate reader. The result for anticoagulant activity was found
to be 36 seconds for control, 114 seconds for wild-type aPC, and 108 seconds for L194S aPC.
Amidolytic activity was found to be N/A mM/second for control, 98 mM/second for wild-type
aPC, and 84 mM/second for L194S aPC.; USE - (I) is useful for treating vascular occlusive
disorders, hypercoagulable states such as sepsis, disseminated intravascular coagulation,
purpura fulminans, major trauma, major surgery, burns, adult respiratory distress syndrome,
transplantation, deep vein thrombosis, heparin-induced thrombocytopenia, sickle cell
disease, thalassemia, viral hemorrhagic fever, thrombotic thrombocytopenic purpura, and
hemolytic uremic syndrome, and also useful for treating thrombotic disorders and acute
coronary syndromes such as myocardial infarction, unstable angina, and stroke.; ADVANTAGE -
Protein C derivatives with amino acid substitutions result in increased resistance to
inactivation by serpins when compared to wild-type activated human protein C. They also have
longer half-lives in human blood and hence require either less frequent administration
and/or smaller dosage than wild type human protein C for treating disorders.

L7: Entry 23 of 44

File: DWPI

Nov 9, 2000

DERWENT-ACC-NO: 2001-007227
DERWENT-WEEK: 200101
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Protein C derivatives, useful for treating vascular occlusive disorder, hypercoagulable state, thrombotic disorder and disease states predisposing thrombosis, comprises specific amino acid substitutions

ABTX:
(9) treating thrombotic and vascular occlusive disorders or, hypercoagulable states by inhibiting
binding of activated protein C polypeptides to inhibitor recognition sequences of serpins, PCI and alpha -I-AT.

24. Document ID: WO 200062068 A1
L7: Entry 24 of 44

File: DWPI

Oct 19, 2000

DERWENT-ACC-NO: 2000-679516
DERWENT-WEEK: 200066
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TITLE: Typing, diagnoses, prevention and/or treatment of prion disease
e.g. spongiform encephalopathies using binding of metal ions to PrP(SC)

PRIORITY-DATA: 1999GB-0008059 (April 9, 1999)

PATENT-FAMILY:
PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

WO 200062068 A1

October 19, 2000

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049

G01N033/569

APPLICATION-DATA:
PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

WO 200062068 A1

April 7, 2000

2000WO-GB01327

N/A

INT-CL (IPC): C07K 14/47; G01N 33/569; G01N 33/68

IN: COLLINGE, J, WADSWORTH, J D F

AB: NOVELTY - Typing PrPsc comprises (a) treating a sample containing a PrPsc protein
to remove one or more bound metal ions from PrPsc; (b) digesting PrPsc protein; and (c)
comparing the products of the digestion with the products of a control method in which the
sample is not treated to remove bound metal ions, any difference being indicative of the
presence of type 1 or type 2 PrPsc and no difference being indicative of type 3 or type 4
PrPsc.; DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (i) a
method of altering the conformation of PrPsc comprising treating PrPsc with an agent which
affects the binding of PrPsc to one or more divalent metal ions; (ii) use of an agent
capable of affecting the binding of PrPsc to one or more divalent metal ions in the
manufacture of a composition for use in the prevention, treatment and/or diagnosis of a
prion disease; (iii) a method for screening for an agent capable of altering

the conformation of type 1 and/or type 2 PrPsc comprising (a) exposing type 1 and/or type 2 PrPsc to the agent; (b) digesting the PrPsc; (c) comparing the digestion products with products produced under the same conditions in the absence of the agent, a difference being indicative of a change in the conformation of type 1 and/or type 2 PrPsc; (iv) a method for screening for an agent for use in the diagnosis, prevention and/or treatment of a prion disease comprising testing an agent for its ability to convert type 1 PrPsc to type 2 PrPsc or type 2- PrPsc or vice versa and/or type 2 PrPsc to type 2- PrPsc or vice versa; (v) isolated PrPsc type 2- which when digested produces the same digestion products as type 1 and/or type 2 PrPsc which have been treated prior to digestion to remove one or more bound metal ions; and (vi) use of isolated PrPsc type 2- in the manufacture of a medicament for use in the manufacture of a composition for use in the diagnosis, prevention and/or treatment of a prion disease., ACTIVITY - Neuroprotective., MECHANISM OF ACTION - None given., USE - For typing, diagnoses, prevention and/or treatment of prion disease e.g. spongiform encephalopathies such as Creutzfeldt-Jakob disease and bovine spongiform encephalopathy.

L7: Entry 24 of 44

File: DWPI

Oct 19, 2000

DERWENT-ACC-NO: 2000-679516
DERWENT-WEEK: 200066
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TITLE: Typing, diagnoses, prevention and/or treatment of prion disease e.g. spongiform encephalopathies using binding of metal ions to PrP(SC)

ABTX:
NOVELTY - Typing PrPsc comprises (a) treating a sample containing a PrPsc protein to remove one or more bound metal ions from PrPsc; (b) digesting PrPsc protein; and (c) comparing the products of the digestion with the products of a control method in which the sample is not treated to remove bound metal ions, any difference being indicative of the presence of type 1 or type 2 PrPsc and no difference being indicative of type 3 or type 4 PrPsc.

25. Document ID: AU 9959013 A, WO 200010609 A1
L7: Entry 25 of 44

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031
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TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or diagnosis of cardiovascular disease, by targeting the endothelial cell protein C receptor

PRIORITY-DATA: 1998US-0139425 (August 25, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9959013 A	March 14, 2000	N/A	000	A61K045/06

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200010609 A1	March 2, 2000	E	023	A61K045/06

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 9959013A	August 25, 1999	1999AU-0059013	N/A
AU 9959013A		WO 200010609	Based on
WO 200010609A1	August 25, 1999	1999WO-US19480	N/A

INT-CL (IPC): A61K 45/06

IN: ESMON, C T, XU, J

AB: NOVELTY - A method of selectively delivering molecules (I) to the nucleus of endothelial cells of large vessels by administering a conjugate (C) of (I) with an agent (II) that binds selectively to endothelial protein C receptor (EPCR)., DETAILED DESCRIPTION
- An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not a diagnostic label, with either protein C, optionally activated, or an antibody reactive with EPCR, or fragments of it which bind EPCR., ACTIVITY - Antithrombotic; fibrinolytic; antiinflammatory; anticoagulant; vasoconstrictor., MECHANISM OF ACTION - EPCR translocates from the plasma membrane to the nucleus, and transports molecules that bind to it., USE - (C) are used to deliver therapeutic agents, e.g. nucleic acids, proteins, expression inhibitors, anti-inflammatories, anticoagulants, growth hormones etc., or diagnostic agents such as radiolabels, fluorescent labels and enzymatic labels, particularly in the cases of cardiovascular disease. Typical applications include preventing thrombosis, increasing fibrinolytic activity, or inhibiting leukocyte adhesion., ADVANTAGE - Since EPCR is present mainly on endothelial cells of large vessels, rather than similar cells in capillaries or other small vessels, especially in arteries, using it as target provides selective delivery of (I) with reduced risks of systemic complications. Serum stimulates nuclear translocation of EPCR, so delivery is enhanced during inflammatory or coagulative processes, often present in the treated subjects.

L7: Entry 25 of 44

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031
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TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or diagnosis of cardiovascular disease, by targeting the endothelial cell protein C receptor

ABTX:

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not a diagnostic label, with either protein C, optionally activated, or an antibody reactive with EPCR, or fragments of it which bind EPCR.

26. Document ID: EP 994946 A1, WO 9909164 A1, AU 9892928 A
L7: Entry 26 of 44

File: DWPI

Apr 26, 2000

DERWENT-ACC-NO: 1999-190163
DERWENT-WEEK: 200025
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TITLE: New coding sequence haplotypes of the human BRCA2 gene - used to develop products for determining susceptibility to, detection and treatment of breast or ovarian cancer

PRIORITY-DATA: 1998US-0084471 (May 22, 1998), 1997US-0055784 (August 15, 1997), 1997US-0064926 (November 7, 1997), 1997US-0065367 (November 12, 1997), 1998US-0071715 (May 1, 1998)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

EP 994946 A1

April 26, 2000

E

000

C12N015/12

WO 9909164 A1

February 25, 1999

E

215

C12N015/12

AU 9892928 A

March 8, 1999

N/A

000

C12N015/12

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

EP 994946A1

August 14, 1998

1998EP-0945756

N/A

EP 994946A1

August 14, 1998

1998WO-US16905

N/A

EP 994946A1

WO 9909164

Based on

WO 9909164A1

August 14, 1998

1998WO-US16905

N/A

AU 9892928A

August 14, 1998

1998AU-0092928

N/A

AU 9892928A

WO 9909164

Based on

INT-CL (IPC): A61K 38/17; A61K 48/00; C07K 14/47; C07K 16/18; C12N 15/12; C12Q 1/68

IN: ESKANDARI, T, JACKSON, G M, MURPHY, P D, OLSON, S J, PARK, M, RABIN, M B, SCHRYER, B, WHITE, M B, YOSHIKAWA, M

AB: NOVELTY - Coding sequence haplotypes of the human BRCA2 gene are new., DETAILED

DESCRIPTION - New genomic DNA contains a BRCA2 gene where the first 12 nucleotides (iii)

beginning exon 5 are 5'-TCCTGTTGTTCT-3' as in sequence (I) (TCCTGTTGTT CTACAATGTA CACATGTAAC ACCACAAAGA GATAAGTCAG), where nt numbers 5782-5790 are GTTTGTGTT as in sequence (IV) of

10485 nt, and where the last 20 nt encoding exon 15 are 5'-CTGCGTGTCTCATAAACAG-3' as in

sequence (II) of 182 nt and the first 20 nt beginning at exon 16 are 5'-CTGTATACGTATGGCGTTTC-3' as in sequence (III) of 188 nt.,

INDEPENDENT CLAIMS are also

included for: (1) a DNA comprising a BRCA2 coding sequence, where nt numbers 643-666 are

CTTAGTGAAAGTCCTGTTGTTCTA and where nt numbers

5782-5790 are GTTTGTGTT; (2) a BRCA2 protein

having the following amino acids (aa) at the following peptide numbers:

289 asparagine, 372

histidine, 894 valine, 991 asparagine, 1852 valine, 1853 cysteine, 1854

valine, 2951 alanine

as in sequence (V) of 3418 aa; (3) a BRCA2 protein having the following

aa at the following

peptide numbers: 289 asparagine, 372 asparagine, 599 serine, 894 valine,

991 asparagine,

2951 alanine; (4) a BRCA2 protein having the following aa at the

following peptide numbers:

289 histidine, 372 histidine, 894 valine, 991 aspartic acid, 2951 alanine as

in sequence

(IX) of 3418 aa; (5) a BRCA2 protein having the following aa at the

following peptide

numbers: 289 histidine, 372 asparagine, 894 isoleucine, 991 aspartic acid,

2951 threonine as

in sequence (XIII) of 3418 aa; (6) a haplotype of BRCA2 coding

sequence (BRCA2(omi1) as in

(IV) or a complementary sequence; (7) a BRCA2 protein comprising an

aa sequence derived from

BRCA2(omi) as in (V); (8) a haplotype of BRCA2 coding sequence

BRCA2(omi2) as in (VI) or a

complementary sequence; (9) a BRCA2 protein comprising an aa

sequence derived from

BRCA2(omi2) as in (VII); (10) a haplotype of BRCA2 coding sequence

(BRCA2(omi3) as in (VIII) or

a complementary sequence; (11) a BRCA2 protein comprising an aa

sequence derived from

BRCA2(omi3) as in (IX); (12) a haplotype of BRCA2 coding sequence

(BRCA2(omi4) as in (X) or

a complementary sequence; (13) a BRCA2 protein comprising an aa

sequence derived from

BRCA2(omi4) as in (XI); (14) a haplotype of BRCA2 coding sequence

BRCA2(omi5) as in (XII) or

a complementary sequence; (15) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi5) as in (XIII); (16) an ON primer capable of hybridising to a sample of BRCA2 gene or its respective complementary sequences selected from sequences given in the specification;

(17) a chip array having n elements for performing allele specific sequence-based techniques comprising a solid phase chip and oligonucleotides (ONs) having n different nt sequences (NSs), where n at least 10, where the ONs are bound to the solid phase chip in a manner which permits the ONs to hybridise to complementary ONs or polynucleotides (PNs), where ONs having different NS are bound to the solid phase chip at different locations so that a particular location on the solid phase chip exclusively binds ONs having a specific NS, and where at least 10 ONs are capable of specifically hybridising to the BRCA2 DNA having a sequence as in sequence (IV), (VI), (VIII), (X), (XII) or their respective complementary sequences, at least one ON being capable of specifically hybridising at each of the nt positions 1093, 1342, 1593, 2457, 2908, 3199, 3624, 4035, 7470, 9079 or complements; (18) a method of performing gene therapy on a patient comprising: (a) contacting cancer cells in vivo with a vector comprising DNA containing at least a portion of BRCA2 sequence selected from sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; (b) allowing the vector to enter the cancer cells; and (c) measuring a reduction in tumour growth; (19) a method of performing gene therapy on a patient or a sample comprising: (a) contacting cells in vivo or in vitro with a vector comprising DNA containing at least a portion of BRCA2 sequence selected from sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; and (b) allowing the vector to enter the cells; where the patient has a reduced susceptibility for developing a cancer associated with a mutation in the BRCA2 gene; (20) a method of treating a patient suspected of having a tumour comprising: (a) administering to a patient a BRCA2 tumor growth inhibitor having an aa sequence selected from sequence (V), (VII), (IX), (XI), (XIII) or fragments or functional equivalents; (b) allowing the patients cells to take up the protein; and (c) measuring a reduction in tumor growth; (21) a method of preventing the formation or growth of a tumor comprising: (a) administering to a patient a BRCA2 tumour growth inhibiting protein having an aa sequence selected from sequences (V), (VII), (IX), (XI), (XIII) or fragments or functional equivalents; and (b) allowing the patient cells to take up the protein; (22) a cloning vector comprising: (a) a DNA sequence (IV), (VI), (VIII), (X), (XII) or any fragment; and (b) one or more suitable regulatory sequences to induce replication and/or integration in a host cell; (23) an expression vector comprising a DNA sequence as in sequences (IV), (VI), (VIII), (X), (XII) or any fragments operatively linked to one or more promoter sequences capable of directing expression of the sequence in a host cell; (24) a host cell transformed with a vector as in (22) or (23); (25) a BRCA2 polypeptide which is selected from: (a) a fragment of BRCA2 protein sequence as in sequence (V), (VII), (IX), (XI), or (XIII); (b) an aa sequence which is homologous to the BRCA2 protein sequence as in (V), (VII), (IX), (XI), or (XIII); (c) a molecule which has similar function to the BRCA2

protein; and (d) a fusion protein of (a), (b) or (c); and (26) a diagnostic reagent comprising a molecule selected from: (a) a DNA sequence as in (23); (b) a nucleic acid fragment of (a) comprising at least 10 nt; (c) a sequence which hybridises to (a) or (b); (d) a polypeptide as in (2)-(5), (7), (9), (13), (15), or (25) in a carrier.,

USE - The products and methods can be used for identifying mutations in the BRCA2 gene leading to predisposition or higher susceptibility to breast or ovarian cancer. They can also be used for detection and gene therapy for breast and ovarian cancers. They can be used in methods for monitoring disease progression, for determining patients suited for gene and protein replacement progression, or for detecting the presence or quantifying the amount of a tumour growth inhibitor following such therapy. The BRCA2 protein, polypeptides, their functional equivalents, antibodies, and PNs may also be useful in the study of the characteristics of BRCA2 proteins, such as structure and function of BRCA2 in oncogenesis or subcellular localisation of BRCA2 protein in normal and cancerous cells.

L7: Entry 26 of 44

File: DWPI

Apr 26, 2000

DERWENT-ACC-NO: 1999-190163
DERWENT-WEEK: 200025
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TITLE: New coding sequence haplotypes of the human BRCA2 gene - used to develop products for determining susceptibility to, detection and treatment of breast or ovarian cancer

ABTX:
INDEPENDENT CLAIMS are also included for: (1) a DNA comprising a BRCA2 coding sequence, where nt numbers 643-666 are CTTAGTGAAAGTCCTGTTGTCTA and where nt numbers 5782-5790 are GTTTGTGTT; (2) a BRCA2 protein having the following amino acids (aa) at the following peptide numbers: 289 asparagine, 372 histidine, 894 valine, 991 asparagine, 1852 valine, 1853 cysteine, 1854 valine, 2951 alanine as in sequence (V) of 3418 aa; (3) a BRCA2 protein having the following aa at the following peptide numbers: 289 asparagine, 372 asparagine, 599 serine, 894 valine, 991 asparagine, 2951 alanine; (4) a BRCA2 protein having the following aa at the following peptide numbers: 289 histidine, 372 histidine, 894 valine, 991 aspartic acid, 2951 alanine as in sequence (IX) of 3418 aa; (5) a BRCA2 protein having the following aa at the following peptide numbers: 289 histidine, 372 asparagine, 894 isoleucine, 991 aspartic acid, 2951 threonine as in sequence (XIII) of 3418 aa; (6) a haplotype of BRCA2 coding sequence (BRCA2(omi1) as in (IV) or a complementary sequence; (7) a BRCA2 protein comprising an aa sequence derived from BRCA2 (omi1) as in (V); (8) a haplotype of BRCA2 coding sequence BRCA2(omi2) as in (VI) or a complementary sequence; (9) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi2) as in (VII); (10) a haplotype of BRCA2 coding sequence (BRCA2(omi3) as (VIII) or a complementary sequence; (11) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi3) as in (IX); (12) a haplotype of BRCA2 coding sequence (BRCA2(omi4)) as in (X) or a complementary sequence; (13) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi4) as in (XI); (14) a haplotype of

BRCA2 coding sequence BRCA2(omi5) as in (XII) or a complementary sequence; (15) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi5) as in (XIII); (16) an ON primer capable of hybridising to a sample of BRCA2 gene or its respective complementary sequences selected from sequences given in the specification; (17) a chip array having n elements for performing allele specific sequence-based techniques comprising a solid phase chip and oligonucleotides (ONs) having n different nt sequences (NSs), where n at least 10, where the ONs are bound to the solid phase chip in a manner which permits the ONs to hybridise to complementary ONs or polynucleotides (PNs), where ONs having different NS are bound to the solid phase chip at different locations so that a particular location on the solid phase chip exclusively binds ONs having a specific NS, and where at least 10 ONs are capable of specifically hybridising to the BRCA2 DNA having a sequence as in sequence (IV), (VI), (VIII), (X), (XII) or their respective complementary sequences, at least one ON being capable of specifically hybridising at each of the nt positions 1093, 1342, 1593, 2457, 2908, 3199, 3624, 4035, 7470, 9079 or complements; (18) a method of performing gene therapy on a patient comprising: (a) contacting cancer cells in vivo with a vector comprising DNA containing at least a portion of BRCA2 sequence selected from sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; (b) allowing the vector to enter the cancer cells; and (c) measuring a reduction in tumour growth; (19) a method of performing gene therapy on a patient or a sample comprising: (a) contacting cells in vivo or in vitro with a vector comprising DNA containing at least a portion of BRCA2 sequence selected from sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; and (b) allowing the vector to enter the cells; where the patient has a reduced susceptibility for developing a cancer associated with a mutation in the BRCA2 gene; (20) a method of treating a patient suspected of having a tumour comprising: (a) administering to a patient a BRCA2 tumor growth inhibitor having an aa sequence selected from sequence (V), (VII), (IX), (XI), (XIII) or fragments or functional equivalents; (b) allowing the patients cells to take up the protein; and (c) measuring a reduction in tumor growth; (21) a method of preventing the formation or growth of a tumor comprising: (a) administering to a patient a BRCA2 tumour growth inhibiting protein having an aa sequence selected from sequences (V), (VII), (IX), (XI), (XIII) or fragments or functional equivalents; and (b) allowing the patient cells to take up the protein; (22) a cloning vector comprising: (a) a DNA sequence (IV), (VI), (VIII), (X), (XII) or any fragment; and (b) one or more suitable regulatory sequences to induce replication and/or integration in a host cell; (23) an expression vector comprising a DNA sequence as in sequences (IV), (VI), (VIII), (X), (XII) or any fragments operatively linked to one or more promoter sequences capable of directing expression of the sequence in a host cell; (24) a host cell transformed with a vector as in (22) or (23); (25) a BRCA2 polypeptide which is selected from: (a) a fragment of BRCA2 protein sequence as in sequence (V), (VII), (IX), (XI), or (XIII); (b) an aa sequence which is homologous to the BRCA2 protein sequence as in (V), (VII), (IX), (XI), or (XIII); (c) a molecule which has similar function to the BRCA2 protein; and (d) a fusion protein of (a), (b) or (c); and (26) a diagnostic reagent comprising a molecule selected from: (a) a DNA sequence as in (23); (b) a

nucleic acid fragment of (a) comprising at least 10 nt; (c) a sequence which hybridises to (a) or (b); (d) a polypeptide as in (2)-(5), (7), (9), (13), (15), or (25) in a carrier.

27. Document ID: EP 1003783 A2, WO 9907736 A2, FR 2767135 A1, FR 2767136 A1, AU 9885563 A
L7: Entry 27 of 44

File: DWPI

May 31, 2000

DERWENT-ACC-NO: 1999-167364
DERWENT-WEEK: 200031
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TITLE: Use of lipolysis stimulated receptor - for developing agents for modulating partitioning of dietary lipids between the liver and peripheral tissues, e.g. for treating obesity

PRIORITY-DATA: 1998FR-0005032 (April 22, 1998), 1997FR-0010088 (August 6, 1997)

PATENT-FAMILY:
PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1003783 A2 May 31, 2000	E	000	C07K014/715
WO 9907736 A2 February 18, 1999	E	076	C07K014/00
FR 2767135 A1 February 12, 1999	N/A	000	C07K014/705
FR 2767136 A1 February 12, 1999	N/A	000	C07K014/715
AU 9885563 A March 1, 1999	N/A	000	C07K014/00

APPLICATION-DATA:
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
EP 1003783A2 August 6, 1998	1998EP-0936610	N/A
EP 1003783A2 August 6, 1998	1998WO-IB01256	N/A
EP 1003783A2	WO 9907736	Based on

WO 9907736A2
August 6, 1998
1998WO-1B01256
N/A

FR 2767135A1
April 22, 1998
1998FR-0005032
N/A

FR 2767136A1
August 6, 1997
1997FR-0010088
N/A

AU 9885563A
August 6, 1998
1998AU-0085563
N/A

AU 9885563A
WO 9907736
Based on

INT-CL (IPC): A01K 67/027; A61K 38/17; A61K 38/19; A61K 39/395; A61K 48/00; C07K 14/00; C07K 14/47; C07K 14/705; C07K 14/715; C07K 16/28; C12N 5/10; C12N 15/12; C12N 15/85; C12Q 1/68; G01N 33/68

IN: BIHAIN, B, BOUGUELERET, L, YEN-POTIN, F, YEN, P F

AB: NOVELTY - Agents which influence the partitioning of dietary lipids between the liver and peripheral tissues for use as medicaments. 7 polypeptide sequences (the sequences relate to complement C1qA, complement C1qB, complement C1qC, multimerin, cerebellin, ApM1, AdipoQ and acrp30) and two consensus sequences are given in the specification and are potentially useful as these agents., DETAILED DESCRIPTION - An agent is claimed which influences the partitioning of dietary lipids between the liver and peripheral tissues for use as a medicament., INDEPENDENT CLAIMS are included for: (1) a polypeptide comprising a consensus sequence selected from sequence (I): PheX(5) [AsnAsp]X(4) [PheTyrTrpLeu]X(6) PheX(5)GlyXTyrXPhe X[PheTyr] and (II): [SerThr]XPhe[SerThr] Gly[PheTyr]Leu[LeuVal] [PheTyr] for use as a medicament; (2) a polypeptide comprising an amino acid sequence selected from polypeptides having at least 25%, 50% or 80% homology to one of the sequences (VII)-(XIV) given in the specification, for use as a medicament; (3) a C1q polypeptide, derivative, homologue or a fragment of any of the preceding compounds for use as a medicament; (4) an AdipoQ polypeptide or a derivative, homologue or fragment for use as a medicament; (5) an ApM1 polypeptide, derivative, homologue or fragment for use as a medicament; (6) a composition for modulating the activity of LSR comprising a compound having binding specificity for the gC1q.R protein, where the compound is not a subunit of the LSR; and a carrier; (7) a method of reducing plasma lipoprotein levels in an animal comprising: (a) identifying an animal having a measurable plasma lipoprotein level; (b) administering to the animal a composition that includes a carrier and a polypeptide that is at least 25% homologous to an ApM1 protein; and (c) allowing passage of a period of time to permit reduction in the measurable plasma lipoprotein level; (8) a method for treating an animal having a condition in which it is desirable to increase the partitioning of dietary lipids to the liver, comprising administering an LSR agonist to the animal having the condition; (9) a method for treating an animal having a condition in which it is desirable to decrease

the partitioning of dietary lipids to the liver, comprising administering an LSR antagonist to the animal having the condition; (10) an agent which increases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (11) an agent which decreases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (12) a method for decreasing the partitioning of dietary lipids to the liver comprising administering an agent which decreases the activity of a compound selected from adipoQ, ApM1, C1q, compounds comprising at least one sequence selected from sequences (I) and (II), compounds comprising an amino acid sequence having at least 25% homology to a sequence selected from sequences (VII)-(XIV) given in the specification, (129, 130, 124, 130, 130, 130, 130, and 126 amino acids respectively), polypeptides comprising an amino acid sequence having at least 50% homology to a sequence selected from sequences (VII)-(XIV), and polypeptides comprising an amino acid sequence having at least 80% homology to a sequence selected from sequences (VII)-(XIV)., USE - Compounds that influences the partitioning of dietary lipids between the liver and peripheral tissues can be used in medicament for treating a condition in which the partitioning of dietary lipids to the liver is abnormal (claimed). A polypeptide having binding specificity for a gamma subunit of the lipolysis stimulated receptor (LSR) or a gC1q.R or a gC1q.R homologue can be used for treatment of obesity, where the polypeptide is not a subunit of the LSR (claimed). The agents which increase partitioning of dietary lipids to the liver can be used for treating obesity-related atherosclerosis, obesity-related insulin resistance, obesity-related hypertension, microangiopathic lesions resulting from obesity-related Type II diabetes, ocular lesions caused by microangiopathy in obese individuals with Type II diabetes, and renal lesions caused by microangiopathy in obese individuals with Type II diabetes (claimed). Agents which decrease the partitioning of dietary lipids to the liver can be used for treating cachexia in subjects with, neoplastic or para-neoplastic syndrome or eating disorders (claimed)., Studies showed that gC1q-R has a sequence analogous to LSR. Incubation of rat hepatocytes with C1q led to activation of Lipolysis stimulated receptor (LSR). The effect of C1q led to the investigation of proteins sharing structured homology to C1q. The murine proteins AdipoQ and the human ApM1 protein clearly exhibited marked homologies. Recombinant AdipoQ was shown to stimulate LSR activity in cultured rat hepatocytes. Agents which modify the structure of the LSR complex by perturbing interaction of the gamma subunit with the LSR activate the LSR in the absence of free fatty acids The effect of this perturbation can be measured as increased hepatocyte binding, internalisation and degradation of lipoproteins.

L7: Entry 27 of 44

File: DWPI

May 31, 2000

DERWENT-ACC-NO: 1999-167364
DERWENT-WEEK: 200031
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TITLE: Use of lipolysis stimulated receptor - for developing agents for modulating partitioning of dietary lipids between the liver and peripheral tissues, e.g. for treating obesity

ABTX:
INDEPENDENT CLAIMS are included for: (I) a polypeptide comprising a consensus sequence selected from sequence (I): PheX(5) [AsnAsp]X(4) [PheTyrTrpLeu]X(6) PheX(5)GlyXTyrX[PheTyr] and (II): [SerThr]XPhe[SerThr] Gly[PheTyr]Leu[LeuVal] [PheTyr] for use as a medicament; (2) a polypeptide comprising an amino acid sequence selected from polypeptides having at least 25%, 50% or 80% homology to one of the sequences (VII)-(XIV) given in the specification, for use as a medicament; (3) a C1q polypeptide, derivative, homologue or a fragment of any of the preceding compounds for use as a medicament; (4) an AdipoQ polypeptide or a derivative, homologue or fragment for use as a medicament; (5) an ApM1 polypeptide, derivative, homologue or fragment for use as a medicament; (6) a composition for modulating the activity of LSR comprising a compound having binding specificity for the gC1q.R protein, where the compound is not a subunit of the LSR; and a carrier; (7) a method of reducing plasma lipoprotein levels in an animal comprising: (a) identifying an animal having a measurable plasma lipoprotein level; (b) administering to the animal a composition that includes a carrier and a polypeptide that is at least 25% homologous to an ApM1 protein; and (c) allowing passage of a period of time to permit reduction in the measurable plasma lipoprotein level; (8) a method for treating an animal having a condition in which it is desirable to increase the partitioning of dietary lipids to the liver, comprising administering an LSR agonist to the animal having the condition; (9) a method for treating an animal having a condition in which it is desirable to decrease the partitioning of dietary lipids to the liver, comprising administering an LSR antagonist to the animal having the condition; (10) an agent which increases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (11) an agent which decreases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (12) a method for decreasing the partitioning of dietary lipids to the liver comprising administering an agent which decreases the activity of a compound selected from adipoQ, ApM1, C1q, compounds comprising at least one sequence selected from sequences (I) and (II), compounds comprising an amino acid sequence having at least 25% homology to a sequence selected from sequences (VII)-(XIV) given in the specification, (129, 130, 124, 130, 130, 130, 130, and 126 amino acids respectively), polypeptides comprising an amino acid sequence having at least 50% homology to a sequence selected from sequences (VII)-(XIV), and polypeptides comprising an amino acid sequence having at least 80% homology to a sequence selected from sequences (VII)-(XIV).

28. Document ID: US 5948639 A, WO 9845467 A1, AU 9869681 A
L7: Entry 28 of 44

File: DWPI

Sep 7, 1999

DERWENT-ACC-NO: 1998-583204
DERWENT-WEEK: 199943
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TITLE: Nucleic acid encoding endothelial MAD interactor I - for modulating cell proliferation and differentiation, e.g. in cases of atherosclerosis and cancer of colon or pancreas

PRIORITY-DATA: 1997US-0844312 (April 10, 1997)

PATENT-FAMILY:
PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

US 5948639 A	September 7, 1999	N/A	000	C12P021/00
WO 9845467 A1	October 15, 1998	E	095	C12P021/00
AU 9869681 A	October 30, 1998	N/A	000	C12P021/00

APPLICATION-DATA:
PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

US 5948639A	April 10, 1997	1997US-0844312	N/A
WO 9845467A1	April 10, 1998	1998WO-US07356	N/A
AU 9869681A	April 10, 1998	1998AU-0069681	N/A
AU 9869681A		WO 9845467	Based on

INT-CL (IPC): A61K 38/18; C07H 21/04; C07K 14/46; C12N 1/21; C12N 5/10; C12N 15/00; C12N 15/12; C12P 21/00

IN: FALB, D A, GIMENO, C J

AB: New isolated nucleic acid (I) encodes EMII (endothelial mothers against dpp (MAD) (sic) interactor I), or biologically active parts of it, or its homologues that are able to modulate a TGF beta (transformin g growth factor) response in TGF beta responsive cells.

Also new are: (1) isolated nucleic acid (Ia) of at least 15 nucleotides (nt) that hybridise to a 1290 bp sequence (I) reproduced, or to the DNA insert of ATCC 98375; (2) isolated nucleic acid (Ib) encoding an EMII fusion protein (II); (3) nucleic acid (Ic) antisense to (I); (4) vectors containing (I); (5) host cells containing such vectors; (6) isolated EMII protein (III), its fragments or homologues that can modulate a TGF beta response; (7)

fusion protein (II);, (8) antigenic EMII peptides of at least 8 amino acids (aa) including an epitope; (9) antibodies (Ab) specific for EMII; (10) non-human transgenic animals containing cells having an EMII gene or homologously recombinant animals containing cells having an altered EMII gene; (11) processes for identifying compounds that: (a) can be used to treat disorders characterised by aberrant EMII expression or activity, (b) bind to EMII protein or (c) inhibit interaction of EMII with a target molecule; USE - MAD proteins have been implicated in the transforming growth factor beta (TGF- beta) cell signalling pathways. Cells as in (5) are used to produce recombinant EMII, used to raise Ab (for use as immunoassay or affinity purification reagents, also therapeutically); for drug screening and to treat EMII deficiency. Compounds identified in (11) are used to modulate cell activities (e.g. proliferation and differentiation), particularly in cells (endothelial or epithelial) that respond to TGF beta through a signalling pathway that involves EMII, especially for treatment of cardiovascular disease (specifically atherosclerosis but also ischaemia/reperfusion, hypertension, restenosis and arterial inflammation) or proliferative diseases, especially cancer of gut-derived cells, e.g. colorectal or pancreatic cancer, also to modulate angiogenesis, treat autoimmune disease or fibrosis and to regulate wound healing. Primers and probes based on (I), and Ab, are used to detect EMII RNA, or protein, in standard assays, also to identify and clone EMII homologues, while detection of changes in the EMII g ene is used to assess risk of disease associated with aberrant EMII expression or activity. The animals as in (10) are useful for drug screening., New isolated nucleic acid (I) encodes EMII (endothelial mothers against dpp (MAD) (sic) interactor I), or biologically active parts of it, or its homologues that are able to modulate a TGF beta (transformin g growth factor) response in TGF beta responsive cells., Also new are: (1) isolated nucleic acid (Ia) of at least 15 nucleotides (nt) that hybridise to a 1290 bp sequence (1) reproduced, or to the DNA insert of ATCC 98375; (2) isolated nucleic acid (Ib) encoding an EMII fusion protein (II); (3) nucleic acid (Ic) antisense to (I); (4) vectors containing (I); (5) host cells containing such vectors; (6) isolated EMII protein (III), its fragments or homologues that can modulate a TGF beta response; (7) fusion protein (II); (8) antigenic EMII peptides of at least 8 amino acids (aa) including an epitope; (9) antibodies (Ab) specific for EMII; (10) non-human transgenic animals containing cells having an EMII gene or homologously recombinant animals containing cells having an altered EMII gene; (11) processes for identifying compounds that: (a) can be used to treat disorders characterised by aberrant EMII expression or activity, (b) bind to EMII protein or (c) inhibit interaction of EMII with a target molecule; USE - MAD proteins have been implicated in the transforming growth factor beta (TGF- beta) cell signalling pathways. Cells as in (5) are used to produce recombinant EMII, used to raise Ab (for use as immunoassay or affinity purification reagents, also therapeutically); for drug screening and to treat EMII deficiency. Compounds identified in (11) are used to modulate cell activities (e.g. proliferation and differentiation), particularly in cells (endothelial or

epithelial) that respond to TGF beta through a signalling pathway that involves EMII, especially for treatment of cardiovascular disease (specifically atherosclerosis but also ischaemia/reperfusion, hypertension, restenosis and arterial inflammation) or proliferative diseases, especially cancer of gut-derived cells, e.g. colorectal or pancreatic cancer, also to modulate angiogenesis, treat autoimmune disease or fibrosis and to regulate wound healing. Primers and probes based on (I), and Ab, are used to detect EMII RNA, or protein, in standard assays, also to identify and clone EMII homologues, while detection of changes in the EMII g ene is used to assess risk of disease associated with aberrant EMII expression or activity. The animals as in (10) are useful for drug screening.

L7: Entry 28 of 44

File: DWPI

Sep 7, 1999

DERWENT-ACC-NO: 1998-583204
DERWENT-WEEK: 199943
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TITLE: Nucleic acid encoding endothelial MAD interactor I - for modulating cell proliferation and differentiation, e.g. in cases of atherosclerosis and cancer of colon or pancreas

ABTX:

(11) processes for identifying compounds that: (a) can be used to treat disorders characterised by aberrant EMII expression or activity, (b) bind to EMII protein or (c) inhibit interaction of EMII with a target molecule.

ABEQ:

(11) processes for identifying compounds that: (a) can be used to treat disorders characterised by aberrant EMII expression or activity, (b) bind to EMII protein or (c) inhibit interaction of EMII with a target molecule.

29. Document ID: EP 889900 A1, WO 9825946 A1, AU 9854283 A
L7: Entry 29 of 44

File: DWPI

Jan 13, 1999

DERWENT-ACC-NO: 1998-348441
DERWENT-WEEK: 199907
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TITLE: New isolated vascular endothelial cadherin-2 - used to develop products for modulating angiogenesis, e.g. for treating tumours, glaucoma, psoriasis, inflammatory diseases or organ transplantation

PRIORITY-DATA: 1996SE-0004731 (December 12, 1996)

PATENT-FAMILY:
PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

EP 889900 A1

January 13, 1999
E
000
C07H021/04
WO 9825946 A1
June 18, 1998
E
053
C07H021/04
AU 9854283 A
July 3, 1998
N/A
000
C07H021/04

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR

EP 889900A1
November 5, 1997
1997EP-0948160
N/A
EP 889900A1
November 5, 1997
1997WO-US20006
N/A
EP 889900A1
WO 9825946
Based on
WO 9825946A1
November 5, 1997
1997WO-US20006
N/A
AU 9854283A
November 5, 1997
1998AU-0054283
N/A
AU 9854283A
WO 9825946
Based on

INT-CL (IPC): A01N 43/04; A61K 38/08; A61K 38/16; A61K 39/395;
C07H 21/04; C07K 14/705; C07K 16/28; C12P
21/08

IN: DEJANA, E, TELO, P

AB: The following are claimed: (A) a glycosylated or unglycosylated protein comprises an amino acid sequence shown or a homologous sequence having at least 70% homology to this sequence; (B) a cDNA sequence coding for a protein as in (A); (C) a structural gene coding for a protein as in (A) or a peptide derived from the protein; (D) a recombinant protein or peptide expressed by a structural gene or a fragment of a gene as in (C); (E) an antibody binding specifically to a protein as in (A) or a part of the protein; (F) a modifier of the binding of a protein as in (A); (G) a diagnostic kit comprising as a diagnostic reagent an antibody as in (E) or a modifier as in (F); (H) a transgenic animal or cell overexpressing or lacking a protein as in (A); (I) an antisense oligonucleotide (ON) based on the cDNA sequence as in (B); (J) a monoclonal antibody (MAB) which specifically binds to a VE-cadherin and modifies angiogenesis; (K) a hybridoma cell line producing a MAB as in (J); (L) a polypeptide which comprises an amino acid sequence which is the same as the amino acid sequence of the variable region of a MAB as in (J); (M) a nucleic acid encodes a polypeptide as in (L); (N) a polypeptide which comprises an amino acid

sequence which is the same as the amino acid sequence of the hypervariable region of a MAB as in (J); (O) a nucleic acid that encodes a polypeptide as in (N); (P) a humanised antibody or a fragment comprising a polypeptide as in (N); (Q) modifiers that specifically bind to an amino acid sequence TIDLR YMSP, and (R) a synthetic peptide comprising an amino acid sequence TIDLR YMSP and is capable of affecting angiogenesis. The products can be used with a chemotherapeutic agent, e.g. doxorubicin, cisplatin and taxol., USE - The novel polypeptides are vascular endothelial cadherins (designated VE-cadherin-2) which promote cell-to-cell homotypic adhesion and their expression is upregulated in proliferating endothelial cells in comparison to resting cells. The products can be used for inhibiting angiogenesis and inhibiting pathological conditions such as tumours, neovascular glaucoma, proliferative retinopathy including proliferative diabetic retinopathy, macular degeneration, hemangiomas, angiofibromas, and psoriasis. They can also be used for the prevention or inhibition of leukocyte infiltration, tumour cell metastasis, or endothelial permeability, as vaccines and for making endothelial junctions more permeable to antigens, thus indicating use of the modifiers for treatment or prevention of acute and chronic inflammatory diseases, organ transplantation, myocardial ischaemia, atherosclerosis, rheumatoid arthritis and intestinal infection. The products can also be used for detection, diagnosis and drug screening.

L7: Entry 29 of 44

File: DWP1

Jan 13, 1999

DERWENT-ACC-NO: 1998-348441
DERWENT-WEEK: 199907
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: New isolated vascular endothelial cadherin-2 - used to develop products for modulating angiogenesis, e.g. for treating tumours, glaucoma, psoriasis, inflammatory diseases or organ transplantation

ABTX:

The following are claimed: (A) a glycosylated or unglycosylated protein comprises an amino acid sequence shown or a homologous sequence having at least 70% homology to this sequence; (B) a cDNA sequence coding for a protein as in (A); (C) a structural gene coding for a protein as in (A) or a peptide derived from the protein; (D) a recombinant protein or peptide expressed by a structural gene or a fragment of a gene as in (C); (E) an antibody binding specifically to a protein as in (A) or a part of the protein; (F) a modifier of the binding of a protein as in (A); (G) a diagnostic kit comprising as a diagnostic reagent an antibody as in (E) or a modifier as in (F); (H) a transgenic animal or cell overexpressing or lacking a protein as in (A); (I) an antisense oligonucleotide (ON) based on the cDNA sequence as in (B); (J) a monoclonal antibody (MAB) which specifically binds to a VE-cadherin and modifies angiogenesis; (K) a hybridoma cell line producing a MAB as in (J); (L) a polypeptide which comprises an amino acid sequence which is the same as the amino acid sequence of the variable region of a MAB as in (J); (M) a nucleic acid that encodes a polypeptide as in (L); (N) a polypeptide which comprises an

amino acid sequence
 which is the same as the amino acid sequence of the hypervariable region
 of a MAb as in (J); (O)
 a nucleic acid that encodes a polypeptide as in (N); (P) a humanised
 antibody or a fragment
 comprising a polypeptide as in (N); (Q) modifiers that specifically bind to
 an amino acid
 sequence TIDLRYMSP, and (R) a synthetic peptide comprising an amino
 acid sequence TIDLRYMSP and
 is capable of affecting angiogenesis.

30. Document ID: JP 2000511411 W, WO 9741151 A2, AU 9728182
 A, EP 912608 A2
 L7: Entry 30 of 44

File: DWPI

Sep 5, 2000

DERWENT-ACC-NO: 1997-549682
 DERWENT-WEEK: 200047
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TITLE: New isolated streptococcal choline binding proteins - used to
 develop products for
 treating or preventing bacterial infection and for detection, diagnosis and
 screening

PRIORITY-DATA: 1996US-0642250 (May 1, 1996), 1996US-0016632
 (May 1, 1996)

PATENT-FAMILY:
 PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2000511411 W September 5, 2000	N/A	132	C12N015/09
WO 9741151 A2 November 6, 1997	E	142	C07K014/315
AU 9728182 A November 19, 1997	N/A	000	C07K014/315
EP 912608 A2 May 6, 1999	E	000	C07K014/315

APPLICATION-DATA:
 PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
JP2000511411 W May 1, 1997	1997JP-0539170	N/A
JP2000511411 W May 1, 1997	1997WO-US07198	N/A
JP2000511411 W		

WO 9741151

Based on

WO 9741151A2	May 1, 1997	1997WO-US07198	N/A
AU 9728182A	May 1, 1997	1997AU-0028182	N/A
AU 9728182A		WO 9741151	Based on
EP 912608A2	May 1, 1997	1997EP-0922539	N/A
EP 912608A2	May 1, 1997	1997WO-US07198	N/A
EP 912608A2		WO 9741151	Based on

INT-CL (IPC): A61K 31/14; A61K 31/197; A61K 38/00; A61K 38/43;
 A61K 39/09; A61K 39/395; A61K 45/00; A61K
 48/00; A61P 11/00; A61P 31/04; C07K 14/315; C07K 16/12; C12N 1/21;
 C12N 5/10; C12N 15/02; C12N 15/09; C12P
 21/08 ; C12Q 1/68; G01N 33/53; G01N 33/569; G01N 33/577

IN: MASURE, H R, ROSENOW, C I, TUOMANEN, E,
 WIZEMAN, T M

AB: A new streptococcal choline binding protein (SCBP) has the
 following
 characteristics:(a) choline-binding activity; and (b) elution from a
 chromatographic column
 in the presence of at least about 10% choline; with the proviso that the
 SCBP is not PspA or
 autolysin (LytA). Also claimed are: (1) a SCBP having either a 420 or
 631 amino acid (aa)
 sequence given in the specification; (2) a purified (monoclonal) antibody
 to SCBP; (3) an
 immortal cell line that produces a monoclonal antibody (MAb) as in (2);
 (4) a purified
 (recombinant) nucleic acid (I) which encodes an SCBP as described
 above (sequences given in
 the specification), or a fragment of at least 15 nucleotides; (5) (I)
 operatively linked to
 an expression control sequence; (6) an oligonucleotide prepared from (I)
 that is capable of
 screening for nucleic acid encoding SCBP in alternate species; (7) a
 unicellular host
 transformed with a recombinant DNA molecule as in (5); (8) a
 pharmaceutical composition
 comprising an inhibitor of streptococcal adhesion to fibronectin selected
 from a peptide of
 not more than 15 amino acid residues containing the aa sequence
 WQPPRARI, an enolase, and an
 antibody specific for the aa sequence WQPPRARI; (9) a method for
 treating infection with a
 bacterium that expressed a SCBP comprising administering a hindered
 cationic small molecule
 that inhibits streptococcal adhesion to fibronectin; (10) a method for
 treating infection
 with a bacterium that expresses an SCBP comprising administering
 pulmonarily an adhesion
 inhibitory agent selected from: (a) an SCBP with the proviso that the
 SCBP is not PspA or
 autolysin (LytA); (b) an antibody to a choline binding protein; (c) an
 enolase; (d) a
 hindered cationic small molecule; (e) the peptide WQPPRARI; and (f) an
 antibody specific for
 an epitope having the aa sequence WQPPRARI. USE - The SCBPs can
 be used in vaccines. They
 can be used for treating or preventing bacterial infection. They can also

be used for
screening, detection and diagnosis. The antibodies can be used for
passive immunisation,
diagnostics, or screening.

L7: Entry 30 of 44

File: DWPI

Sep 5, 2000

DERWENT-ACC-NO: 1997-549682
DERWENT-WEEK: 200047
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: New isolated streptococcal choline binding proteins - used to
develop products for
treating or preventing bacterial infection and for detection, diagnosis and
screening

ABTX:

Also claimed are: (1) a SCBP having either a 420 or 631 amino acid (aa)
sequence given in the
specification; (2) a purified (monoclonal) antibody to SCBP; (3) an
immortal cell line that
produces a monoclonal antibody (MAb) as in (2); (4) a purified
(recombinant) nucleic acid (I)

which encodes an SCBP as described above (sequences given in the
specification), or a fragment of
at least 15 nucleotides; (5) (I) operatively linked to an expression control
sequence; (6) an

oligonucleotide prepared from (I) that is capable of screening for nucleic
acid encoding SCBP in
alternate species; (7) a unicellular host transformed with a recombinant
DNA molecule as in (5);

(8) a pharmaceutical composition comprising an inhibitor of streptococcal
adhesion to fibronectin
selected from a peptide of not more than 15 amino acid residues containing
the aa sequence

WQPPRARI, an enolase, and an antibody specific for the aa sequence
WQPPRARI; (9) a method for
treating infection with a bacterium that expressed a SCBP comprising
administering a hindered

cationic small molecule that inhibits streptococcal adhesion to fibronectin;
(10) a method for
treating infection with a bacterium that expresses an SCBP comprising
administering pulmonarily
an adhesion inhibitory agent selected from: (a) an SCBP with the proviso
that the SCBP is not

PspA or autolysin (LytA); (b) an antibody to a choline binding protein; (c)
an enolase; (d) a
hindered cationic small molecule; (e) the peptide WQPPRARI; and (f) an
antibody specific for an
epitope having the aa sequence WQPPRARI.

31. Document ID: WO 9736614 A1, AU 9724293 A
L7: Entry 31 of 44

File: DWPI

Oct 9, 1997

DERWENT-ACC-NO: 1997-549326
DERWENT-WEEK: 199750
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TITLE: Use of crosslinked Staphylococcal protein A - for treating
auto-immune diseases,
transplant rejection neoplastic diseases or infectious disease such as HIV
infection

PRIORITY-DATA: 1996US-0024802 (March 29, 1996)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

WO 9736614 A1

October 9, 1997

E

100

A61K039/09

AU 9724293 A

October 22, 1997

N/A

000

A61K039/09

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

WO 9736614 A1

March 28, 1997

1997WO-US05277

N/A

AU 9724293 A

March 28, 1997

1997AU-0024293

N/A

AU 9724293 A

WO 9736614

Based on

INT-CL (IPC): A61K 39/02; A61K 39/04; A61K 39/09; A61K 45/00;
A61K 47/04; C07K 14/24; C07K 14/315; C07K
14/35; C07K 17/02; C07K 17/06; C07K 17/14

IN: REISER, R F, TERMAN, D S

AB: The following are claimed: (A) a composition useful for treating
an autoimmune or
neoplastic disease and comprising a mixture of monomeric and
crosslinked polymeric protein A
molecules or a functional derivative of a protein A molecule, where: (a)
the cross-linked
polymer molecule comprises at least 2 monomeric units of protein A or of
the functional
derivative, and (b) at least 10% of the total protein A or functional
derivative in the form
of polymers; (B) a composition useful for treating an autoimmune or
neoplastic disease
comprising a chemically crosslinked polymer of protein A, or of a
functional derivative of
protein A, and having the following characteristics: (a) immunoglobulin
Fc binding activity
is less than half that of native protein A, and (b) immunoglobulin V(H)3
region binding is
more than twice that of native protein A; (C) a method of extracorporeal
treatment of a
subject having an autoimmune or neoplastic disease, where, over a course
of one or more
treatments, plasma of the subject is perfused through a protein A-silica
immunoabsorbent
column to produce a perfusate, and the perfusate is reinfused to the
subject; the
improvement comprising: (a) over the course of one or more treatments,
perfusing plasma of
the subject through the column; (b) at each treatment, measuring the
amount of protein A in
the perfusate prior to the reinfusing; (c) when the amount of total protein
A in the
perfusate is < 2 μ g, increasing the volume of the perfusate or increasing
the number of
doses of the perfusate such that the subject receives 2-200 μ g per
treatment; (d) when the

amount of total protein A in the perfusate is > 200 µg, decreasing the volume of the perfusate such that the subject receives 2-200 µg per treatment; (D) a method of extracorporeal treatment of a subject having an autoimmune or neoplastic disease where, over a course of one or more treatments, plasma of the subject is perfused through a protein A-silica immunoadsorbent column to produce a perfusate, and the perfusate is reinfused to the subject, the improvement comprising: (a) over the course of one or more treatments, perfusing plasma of the subject through the column; (b) at each treatment, measuring the amount of bacterial enterotoxins in the perfusate prior to the reinfusing; (c) when the amount of total bacterial enterotoxins in the perfusate is < 1 ng, increasing the volume of the perfusate or increasing the number of doses of the perfusate such that the subject receives 1-200 ng per treatment; (d) when the amount of total bacterial enterotoxins in the perfusate is > 200 ng, decreasing the volume of the perfusate such that the subject receives 1-200 ng per treatment; and (E) a method for reducing toxicity of monomeric enterotoxin molecules by mixing the enterotoxin molecules with protein A, adding a crosslinking agent capable of crosslinking the enterotoxin molecules and protein A and allowing any enterotoxin to be chemically crosslinked with the protein A, thereby reducing the toxicity. In (A), the polymers have a range of molecular masses 12-10 000 (preferably 64-1000) kDa and at least 50 % of the total protein A or functional derivative is in the form of polymers. The protein A is complexed with IgG and complement components to form protein A-immunoglobulin-complement complexes. The IgG is a monoclonal antibody. The protein A is further crosslinked with molecules of a bacterial superantigen or its functional derivative to form a mixture of: (i) protein A-superantigen; (ii) protein A functional derivative-superantigen; (iii) protein A-superantigen functional derivative, or (iv) protein A functional derivative-superantigen functional derivative, and (c) polymeric crosslinked superantigen or superantigen functional derivative. The bacterial superantigen is selected from: enterotoxin of *Staphylococcus aureus*, toxic shock syndrome toxin, a *Streptococcus pyrogenes* exotoxin, etc. The crosslinking is with e.g. 1-cyclohexyl-3-(2-morpholino-4-ethyl)carbodiimide. USE - The crosslinked *Staphylococcus* protein A (SpA) readily combines with IgG in host plasma to form complexes which bind to and block the FcR on macrophages, lymphocytes and platelets. The compositions can be used for treating autoimmune diseases such as idiopathic thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, Alzheimer's disease, Type I diabetes mellitus, sarcoidosis, vernal conjunctivitis, glomerulonephritis, pemphigus vulgaris, chronic active hepatitis, primary biliary cirrhosis, dermatitis, asthma, transplant rejection, paraneoplastic syndrome or haemolytic anaemia, neoplastic diseases such as carcinomas of the breast, lung, colon or kidney, melanomas, lymphomas or leukaemias and infectious diseases. The compositions can also be used in HIV disorders to prevent gp 120 induced programming of B and T cells for apoptosis. The compositions can also be used in vitro to test products, monitor therapy, and diagnose diseases associated with abnormal function of Fc receptors or abnormal processing

of immune complexes or FcR-binding structures. ADVANTAGE - The complexes are extremely efficient in FcR blocking and can achieve pharmacologic effects at relatively low doses. In the extracorporeal methods, by prescribing the amount of SpA infused, the method avoids toxicity and improves the therapeutic index.

L7: Entry 31 of 44

File: DWPI

Oct 9, 1997

DERWENT-ACC-NO: 1997-549326
DERWENT-WEEK: 199750
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Use of crosslinked *Staphylococcus* protein A - for treating auto-immune diseases, transplant rejection neoplastic diseases or infectious disease such as HIV infection

ABTX:

The following are claimed: (A) a composition useful for treating an autoimmune or neoplastic disease and comprising a mixture of monomeric and crosslinked polymeric protein A molecules or a functional derivative of a protein A molecule, where: (a) the cross-linked polymer molecule comprises at least 2 monomeric units of protein A or of the functional derivative, and (b) at least 10% of the total protein A or functional derivative in the form of polymers; (B) a composition useful for treating an autoimmune or neoplastic disease comprising a chemically crosslinked polymer of protein A, or of a functional derivative of protein A, and having the following characteristics: (a) immunoglobulin Fc binding activity is less than half that of native protein A, and (b) immunoglobulin V(H)3 region binding is more than twice that of native protein A; (C) a method of extracorporeal treatment of a subject having an autoimmune or neoplastic disease, where, over a course of one or more treatments, plasma of the subject is perfused through a protein A-silica immunoadsorbent column to produce a perfusate, and the perfusate is reinfused to the subject; the improvement comprising: (a) over the course of one or more treatments, perfusing plasma of the subject through the column; (b) at each treatment, measuring the amount of protein A in the perfusate prior to the reinfusing; (c) when the amount of total protein A in the perfusate is < 2 µg, increasing the volume of the perfusate or increasing the number of doses of the perfusate such that the subject receives 2-200 µg per treatment; (d) when the amount of total protein A in the perfusate is > 200 µg, decreasing the volume of the perfusate such that the subject receives 2-200 µg per treatment; (D) a method of extracorporeal treatment of a subject having an autoimmune or neoplastic disease where, over a course of one or more treatments, plasma of the subject is perfused through a protein A-silica immunoadsorbent column to produce a perfusate, and the perfusate is reinfused to the subject, the improvement comprising: (a) over the course of one or more treatments, perfusing plasma of the subject through the column; (b) at each treatment, measuring the amount of bacterial enterotoxins in the perfusate prior to the reinfusing; (c) when the amount of total bacterial enterotoxins in the perfusate is < 1 ng, increasing the volume of the perfusate or increasing the number of doses of the perfusate such that the subject receives 1-200 ng per treatment; (d) when the amount of

total bacterial enterotoxins in the perfusate is > 200 ng, decreasing the volume of the perfusate such that the subject receives 1-200 ng per treatment; and (E) a method for reducing toxicity of monomeric enterotoxin molecules by mixing the enterotoxin molecules with protein A, adding a crosslinking agent capable of crosslinking the enterotoxin molecules and protein A and allowing any enterotoxin to be chemically crosslinked with the protein A, thereby reducing the toxicity.

32. Document ID: KR 99082173 A, WO 9728446 A1, AU 9722422 A, EP 922222 A1, JP 2000504114 W
L7: Entry 32 of 44

File: DWPI

Nov 25, 1999

DERWENT-ACC-NO: 1997-402745
DERWENT-WEEK: 200055
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TITLE: Detection and evaluation of bladder cancer - by quantitation of amounts of hyaluronic acid or hyaluronidase in samples such as blood, tissue extract or urine

PRIORITY-DATA: 1996US-0010976 (February 1, 1996)

PATENT-FAMILY:
PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 99082173 A			
November 25, 1999	N/A	000	G01N033/53
WO 9728446 A1			
August 7, 1997	E	126	G01N033/53
AU 9722422 A			
August 22, 1997	N/A	000	G01N033/53
EP 922222 A1			
June 16, 1999	E	000	G01N033/53
JP 2000504114 W			
April 4, 2000	N/A	089	G01N033/574

APPLICATION-DATA:
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
KR 99082173A		
January 31, 1997	1997WO-US00546	N/A
KR 99082173A		
July 31, 1998		

1998KR-0705898
N/A

KR 99082173A

WO 9728446

Based on

WO 9728446A1

January 31, 1997

1997WO-US00546

N/A

AU 9722422A

January 31, 1997

1997AU-0022422

N/A

AU 9722422A

January 31, 1997

1997WO-US00546

N/A

AU 9722422A

WO 9728446

Based on

EP 922222A1

January 31, 1997

1997EP-0905574

N/A

EP 922222A1

January 31, 1997

1997WO-US00546

N/A

EP 922222A1

WO 9728446

Based on

JP2000504114W

January 31, 1997

1997JP-0527660

N/A

JP2000504114W

January 31, 1997

1997WO-US00546

N/A

JP2000504114W

WO 9728446

Based on

INT-CL (IPC): A01N 47/40; A01N 47/46; A01N 47/48; A61K 31/21; A61K 31/26; C12Q 1/34; G01N 33/15; G01N 33/53; G01N 33/537; G01N 33/573; G01N 33/574

IN: BLOCK, N L, LOKESHWAR, V B, PHAM, H T

AB: The following are claimed: (A) screening for bladder cancer (BC), comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronic acid (HA) in the sample; and (c) comparing the normalised amount of HA to a cut-off limit of HA for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HA is greater than the cut-off limit of HA; (B) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronidase (HE) in the sample; and (c) comparing the normalised amount of HE to a cut-off limit of HE for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HE is greater than the cut-off limit of HE; (C) differentiating BC by grade, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating and normalising the amount of HA in the sample; (c) quantitating and normalising the amount of HE in the sample; (d) comparing the normalised amount of HA to a cut-off limit of HA for having BC; (e) comparing the normalised amount of HE to a cut-off limit of HE for having BC; and (f)

identifying the person as having low-grade BC when the normalised amount of HA is greater than the cut-off limit of HA and the normalised amount of HE is less than the cut-off limit of HE, or identifying the person as having intermediate-grade or high grade BC when the normalised amount of HE is greater than the cut off limit of HE; (D) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) separating HA and/or HE in the sample to obtain a size profile; and (c) identifying the person as having increased risk for BC based on the size profile; (E) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) adding the sample to a cell culture; and (c) identifying the person as having increased risk of BC by proliferation of the cell culture; (F) diagnostic kit for detection of BC, comprising: (a) HA; (b) HA binding protein; and (c) ancillary reagents suitable for quantitating HA and/or HE in a sample of biological fluid. Components (a), (b) and (c) are in separate containers; (G) composition comprising an enriched fraction of HE p65 or p55; (H) composition comprising a HA fragment generated by the HE described in (E); (I) composition comprising an antibody to the HE of (E) above; and (J) composition comprising an enriched fraction of HA derived from the urine of a person with BC., USE - The processes utilise the new discovery that HA and HE are diagnostic markers for the detection of bladder cancer (e.g. transitional cell carcinoma, squamous carcinoma and adenocarcinoma), evaluation of its grade, and monitoring the efficacy of its treatment., ADVANTAGE - Measurements of HA and HE levels are simple and are non-invasive, and typically require only a HA-binding protein which can be purified in large quantities.

L7: Entry 32 of 44

File: DWPI

Nov 25, 1999

DERWENT-ACC-NO: 1997-402745
DERWENT-WEEK: 200055
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TITLE: Detection and evaluation of bladder cancer - by quantitation of amounts of hyaluronic acid or hyaluronidase in samples such as blood, tissue extract or urine

ABTX:

The following are claimed: (A) screening for bladder cancer (BC), comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronic acid (HA) in the sample; and (c) comparing the normalised amount of HA to a cut-off limit of HA for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HA is greater than the cut-off limit of HA; (B) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronidase (HE) in the sample; and (c) comparing the normalised amount of HE to a cut-off limit of HE for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HE is greater than the cut-off limit of HE; (C) differentiating BC by grade, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating and normalising the amount of HA in the

sample; (c) quantitating and normalising the amount of HE in the sample; (d) comparing the normalised amount of HA to a cut-off limit of HA for having BC; (e) comparing the normalised amount of HE to a cut-off limit of HE for having BC; and (f) identifying the person as having low-grade BC when the normalised amount of HA is greater than the cut-off limit of HA and the normalised amount of HE is less than the cut-off limit of HE, or identifying the person as having intermediate-grade or high grade BC when the normalised amount of HE is greater than the cut off limit of HE; (D) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) separating HA and/or HE in the sample to obtain a size profile; and (c) identifying the person as having increased risk for BC based on the size profile; (E) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) adding the sample to a cell culture; and (c) identifying the person as having increased risk of BC by proliferation of the cell culture; (F) diagnostic kit for detection of BC, comprising: (a) HA; (b) HA binding protein; and (c) ancillary reagents suitable for quantitating HA and/or HE in a sample of biological fluid. Components (a), (b) and (c) are in separate containers; (G) composition comprising an enriched fraction of HE p65 or p55; (H) composition comprising a HA fragment generated by the HE described in (E); (I) composition comprising an antibody to the HE of (E) above; and (J) composition comprising an enriched fraction of HA derived from the urine of a person with BC.

33. Document ID: AU 707349 B, WO 9605303 A1, AU 9532723 A, EP 777731 A1, US 5695993 A, US 5852171 A
L7: Entry 33 of 44

File: DWPI

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
DERWENT-WEEK: 199938
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor binding, enhance inflammatory response

PRIORITY-DATA: 1994US-0289699 (August 12, 1994), 1997US-0878283 (June 18, 1997)

PATENT-FAMILY:
PUB-NO

PUB-DATE

LANGUAGE
PAGES
MAIN-IPC
000
C12N015/12
058
C12N015/12

AU 707349 B
July 8, 1999

N/A

WO 9605303 A1
February 22, 1996

E

AU 9532723 A

March 7, 1996	N/A	000	C12N015/12
EP 777731 A1			
June 11, 1997	E	000	C12N015/12
US 5695993 A			
December 9, 1997	N/A	028	C12N005/16
US 5852171 A			
December 22, 1998	N/A	000	C07K014/705
APPLICATION-DATA:			
PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 707349B	August 9, 1995	1995AU-0032723	N/A
AU 707349B		AU 9532723	Previous Publ.
AU 707349B		WO 9605303	Based on
WO 9605303A1	August 9, 1995	1995WO-US09636	N/A
AU 9532723A	August 9, 1995	1995AU-0032723	N/A
AU 9532723A		WO 9605303	Based on
EP 777731A1	August 9, 1995	1995EP-0929335	N/A
EP 777731A1	August 9, 1995	1995WO-US09636	N/A
EP 777731A1		WO 9605303	Based on
US 5695993A	August 12, 1994	1994US-0289699	N/A
US 5852171A	August 12, 1994	1994US-0289699	Div ex
US 5852171A	June 18, 1997	1997US-0878283	N/A
US 5852171A		US 5695993	Div ex
INT-CL (IPC): A61K 38/17; A61K 39/395; C07H 21/04; C07K 14/705; C07K 16/28; C12N 5/16; C12N 15/11; C12N 15/12; G01N 33/68			

IN: ESMON, C T, FUKUDOME, K

AB: Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new.

Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
 DERWENT-WEEK: 199938
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TITLE: Isolated endothelial cell protein C/activated protein C receptor -
 used to inhibit
 inflammatory responses, screen for cpds. which alter receptor binding and,
 by blocking receptor
 binding, enhance inflammatory response

ABTX:

USE - EPCR and substances which up-regulate its expression are useful to
 inhibit inflammatory
 responses (claimed). This inhibition is useful in the treatment of, e.g.
 Gram-negative sepsis,
 stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is
 also useful to screen for
 cpds. which alter its binding to (activated) protein C (claimed). Localising
 EPCR to surfaces in
 contact with blood will render the surfaces anticoagulant as EPCR binds
 and concentrates the
 anticoagulant activated protein C at the surface. Its function can also be
 enhanced by
 overexpressing EPCR in endothelium that could be used to coat vascular
 grafts in patients with
 vascular disease, or in stents in cardiac patients. Using blocking cpds. to
 prevent (activated)
 protein C binding to EPCR it is possible to enhance an inflammatory
 response and so treat solid
 tumours.

ABEQ:

USE - EPCR and substances which up-regulate its expression are useful to
 inhibit inflammatory
 responses (claimed). This inhibition is useful in the treatment of, e.g.
 Gram-negative sepsis,
 stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is
 also useful to screen for
 cpds. which alter its binding to (activated) protein C (claimed). Localising
 EPCR to surfaces in
 contact with blood will render the surfaces anticoagulant as EPCR binds
 and concentrates the
 anticoagulant activated protein C at the surface. Its function can also be
 enhanced by
 overexpressing EPCR in endothelium that could be used to coat vascular
 grafts in patients with
 vascular disease, or in stents in cardiac patients. Using blocking cpds. to
 prevent (activated)
 protein C binding to EPCR it is possible to enhance an inflammatory
 response and so treat solid
 tumours.

ABEQ:

USE - EPCR and substances which up-regulate its expression are useful to
 inhibit inflammatory
 responses (claimed). This inhibition is useful in the treatment of, e.g.
 Gram-negative sepsis,
 stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is
 also useful to screen for
 cpds. which alter its binding to (activated) protein C (claimed). Localising
 EPCR to surfaces in
 contact with blood will render the surfaces anticoagulant as EPCR binds
 and concentrates the
 anticoagulant activated protein C at the surface. Its function can also be
 enhanced by
 overexpressing EPCR in endothelium that could be used to coat vascular
 grafts in patients with
 vascular disease, or in stents in cardiac patients. Using blocking cpds. to
 prevent (activated)
 protein C binding to EPCR it is possible to enhance an inflammatory
 response and so treat solid
 tumours.

34. Document ID: AU 710106 B, WO 9534652 A1, AU 9528229 A,
 EP 804580 A1, JP 10504186 W
 L7: Entry 34 of 44

File: DWPI

Sep 16, 1999

DERWENT-ACC-NO: 1996-049681
 DERWENT-WEEK: 199930
 COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Calcium-binding monoclonal antibody immunoreactive with
 Protein C - inhibits Protein C
 anticoagulant activation by thrombin-thrombomodulin, e.g. for treating
 tumours

PRIORITY-DATA: 1994US-0259321 (June 10, 1994)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

AU 710106 B

September 16, 1999

N/A

000

C12N015/13

WO 9534652 A1

December 21, 1995

E

041

C12N015/13

AU 9528229 A

January 5, 1996

N/A

000

C12N015/13

EP 804580 A1

November 5, 1997

E

000

C12N015/13

JP 10504186 W

April 28, 1998

N/A

038

C12N015/09

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

AU 710106B

June 9, 1995

1995AU-0028229

N/A

AU 710106B

AU 9528229

Previous Publ.

AU 710106B

WO 9534652

Based on

WO 9534652A1

June 9, 1995

1995WO-US07372

N/A

AU 9528229A

June 9, 1995

1995AU-0028229

AU 9528229A
 WO 9534652
 Based on
 EP 804580A1
 June 9, 1995
 1995EP-0923791
 N/A
 EP 804580A1
 June 9, 1995
 1995WO-US07372
 N/A
 EP 804580A1
 WO 9534652
 Based on
 JP 10504186W
 June 9, 1995
 1995WO-US07372
 N/A
 JP 10504186W
 June 9, 1995
 1996JP-0502358
 N/A
 JP 10504186W
 WO 9534652
 Based on
 INT-CL (IPC): A61K 33/06; A61K 38/00; A61K 38/19; A61K 39/395;
 A61K 39/395; C07K 16/40; C07K 16/46; C07K
 17/00; C12N 15/09; C12N 15/13; C12P 21/08; A61K 33/06; A61K
 39/395; C12P 21/08; C12R 1/91; A61K 33/06; A61K
 39/395; A61K 38/19; A61K 39/395
 IN: ESMON, C T, REZAIE, A
 AB: A recombinant Ca²⁺ dependent monoclonal antibody (mAb)
 immunoreactive with an
 epitope in the activation peptide region of the heavy chain of Protein C
 defined by (I),
 EDQVDPRLIDKG (I) in combination with calcium, which inhibits
 protein C activation by
 thrombin-thrombomodulin, is claimed., USE - The mAb (opt. with a
 cytokine, or a cytokine
 expression inhibitor to coagulate microvasculature in tumours, but not in
 the absence of the
 mAb) can be used to inhibit Protein C anticoagulant activation by
 thrombin-thrombomodulin
 (claimed), useful in the treatment of tumour patients. The mAb can be
 also be used in
 diagnostic assays (opt. bound to a detectable label), for mimicking HPC-4
 Protein C binding
 and when immobilised on a substrate to purify Protein C from a biological
 fluid (claimed).

L7: Entry 34 of 44

File: DWPI

Sep 16, 1999

DERWENT-ACC-NO: 1996-049681
 DERWENT-WEEK: 199950
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TITLE: Calcium-binding monoclonal antibody immunoreactive with
 Protein C - inhibits Protein C
 anticoagulant activation by thrombin-thrombomodulin, e.g. for treating
 tumours

ABTX:
 USE - The mAb (opt. with a cytokine, or a cytokine expression inhibitor to
 coagulate
 microvasculature in tumours, but not in the absence of the mAb) can be
 used to inhibit Protein C
 anticoagulant activation by thrombin-thrombomodulin (claimed), useful in
 the treatment of tumour
 patients. The mAb can be also be used in diagnostic assays (opt. bound to

a detectable label),
 for mimicking HPC-4 Protein C binding and when immobilised on a
 substrate to purify Protein C
 from a biological fluid (claimed).

35. Document ID: US 5446132A
 L7: Entry 35 of 44

File: DWPI

Aug 29, 1995

DERWENT-ACC-NO: 1995-310936
 DERWENT-WEEK: 199851
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TITLE: New thrombin activated platelet protein-2 - and specific antibodies
 for e.g. detecting
 activated platelets or thromboses and targeting therapeutic agents for
 treating thrombosis

PRIORITY-DATA: 1991US-0086472 (October 1, 1991),
 1991US-0768043 (January 10, 1991)

PATENT-FAMILY:
 PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

US 5446132 A

August 29, 1995

N/A

017

C07K014/435

APPLICATION-DATA:
 PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

US 5446132A

January 10, 1991

1991US-0768043

CIP of

US 5446132A

October 1, 1991

1991US-0086472

N/A

INT-CL (IPC): C07K 14/435; C07K 14/46; C07K 14/47; C07K 14/52

IN: MATSUEDA, G R, REED, G I.

AB: Pure protein, designated thrombin-activated platelet protein-2
 (TAPP-2), that is
 selectively expressed on the surface of thrombin-activated platelets is
 new. It has mol.wt.
 120 kDa and is recognised by an antibody with the binding specificity of
 12A7., USE - TAPP-2
 and the unclaimed protein TAPP-1 are indicators of platelet activation, so
 that their
 presence is indicative of a blood clot. Antibodies (Abs) and their
 fragments are useful in
 immunoassays, for in vivo imaging of thromboses or to target
 immuno-diagnostic or
 immuno-therapeutic agents to thromboses (e.g. using a chimera
 comprising an antigen-binding
 fragment plus a thrombolytic agent, thrombin inhibitor, activated protein
 C etc.). Typical
 applications are the treatment of e.g. pulmonary thromboembolism, deep

venous thrombosis and
renal vein or peripheral arterial thrombosis. Abs are administered at
0.001-50 (esp. 1-10)
picomole/ml, e.g. given orally, intranasally or by injection.

L7: Entry 35 of 44

File: DWPI

Aug 29, 1995

DERWENT-ACC-NO: 1995-310936
DERWENT-WEEK: 199851
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TITLE: New thrombin activated platelet protein-2 - and specific antibodies
for e.g. detecting
activated platelets or thromboses and targetting therapeutic agents for
treating thrombosis

ABTX:

USE - TAPP-2 and the unclaimed protein TAPP-1 are indicators of platelet
activation, so that
their presence is indicative of a blood clot. Antibodies (Abs) and their
fragments are useful in
immunoassays, for in vivo imaging of thromboses or to target
immuno-diagnostic or
immuno-therapeutic agents to thromboses (e.g. using a chimaera
comprising an antigen-binding
fragment plus a thrombolytic agent, thrombin inhibitor, activated protein C
etc.). Typical
applications are the treatment of e.g. pulmonary thromboembolism, deep
venous thrombosis and
renal vein or peripheral arterial thrombosis. Abs are administered at
0.001-50 (esp. 1-10)
picomole/ml, e.g. given orally, intranasally or by injection.

36. Document ID: AU 687116 B, WO 9511314 A1, AU 9480989 A,
US 5445937 A, EP 728216 A1, JP 09504611 W
L7: Entry 36 of 44

File: DWPI

Feb 19, 1998

DERWENT-ACC-NO: 1995-170233
DERWENT-WEEK: 199824
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TITLE: Aiding the diagnosis of Alzheimer's disease - comprises detecting a
disease-specific
biochemical marker macromolecule within a cerebro-spinal fluid or serum
sample

PRIORITY-DATA: 1993US-0138109 (October 20, 1993),
1991US-0812826 (December 24, 1991)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

AU 687116 B

February 19, 1998

N/A

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C12Q001/68

WO 9511314 A1

April 27, 1995

E

067

C12Q001/68

AU 9480989 A

May 8, 1995

N/A

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C12Q001/68

US 5445937 A

August 29, 1995

N/A

026

C12Q001/68

EP 728216 A1

August 28, 1996

E

000

C12Q001/68

JP 09504611 W

May 6, 1997

N/A

055

G01N033/68

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

AU 687116B

October 19, 1994

1994AU-0080989

N/A

AU 687116B

AU 9480989

Previous Publ.

AU 687116B

WO 9511314

Based on

WO 9511314A1

October 19, 1994

1994WO-US11929

N/A

AU 9480989A

October 19, 1994

1994AU-0080989

N/A

AU 9480989A

WO 9511314

Based on

US 5445937A

December 24, 1991

1991US-0812826

CIP of

US 5445937A

October 20, 1993

1993US-0138109

N/A

US 5445937A

US 5272055

CIP of

EP 728216A1

October 19, 1994

1994EP-0931414

N/A

EP 728216A1

October 19, 1994

1994WO-US11929

N/A

EP 728216A1

WO 9511314

Based on

JP09504611 W

October 19, 1994

1994WO-US11929

N/A

JP09504611 W

October 19, 1994

1995JP-0512188

N/A

JP09504611W

WO 9511314

Based on

INT-CL (IPC): C12Q 1/68; G01N 33/573; G01N 33/574; G01N 33/68

IN: HALEY, B E

AB: The following are claimed: (1) a method for aiding in the diagnosis of Alzheimer's disease (AD) in a mammal comprising: (a) contacting in the presence of Mn^{2+} ion a cerebrospinal fluid (CSF) sample which contains a nucleotide binding protein having an apparent mol. wt. of approx. 42000 daltons, where the protein is glutamine synthetase, with an effective amt. of a labelled ATP- or GTP-analogue photoaffinity-labelling reagent which specifically binds the nucleotide binding protein at the nucleotide binding site to photoaffinity label the nucleotide protein; (b) detecting the presence of glutamine synthetase-Ab complexes; and (c) correlating the presence of such complexes with the presence of AD; and (2) methods for aiding in the diagnosis of cancer in a mammal, comprising: (a) contacting a fluid which contains nucleotide binding proteins having apparent mol. wts. of approx. 14 000-15 000, 16 000, 24 000 and 120 000 daltons, with an effective amt. of a labelled ATP- or GTP-analogue photoaffinity-labelling reagent which specifically binds the nucleotide binding protein at the nucleotide binding site to photoaffinity label the nucleotide protein; (b) fractionating the fluid sample to separate the photoaffinity-labelled nucleotide binding protein; (c) detecting the presence of the separated photoaffinity-labelled nucleotide binding protein in normal patients and the absence of the photoaffinity-labelled nucleotide protein in other patients; and (d) correlating the absence of the photo-affinity labelled nucleotide protein to the presence of the relevant disease in the other patients., USE - The methods provide a means of accurately diagnosing AD and cancer esp. leukaemia. The methods may also be used to detect epilepsy, scrapies-type disorders, amyotrophic lateral sclerosis, Down's syndrome, Behcet disease, encephalitis, Huntington's disease, Creutzfeldt-Jakob disease, Parkinson's disease, AIDS dementia, multi-infarct dementia, dystonia, ataxia, schizophrenia, neurosyphilis, cerebral toxoplasmosis, brain irradiation, brain tumour, Guillain-Barre syndrome, tremor, multiple sclerosis, head trauma, acute and chronic encephalitic, vascular disease and eating disorders such as anorexia., ADVANTAGE - The methods incorporate a dual system of comparison in order to diagnose the disease state. Diagnosis is based on both the presence of a unique disease-specific binding protein or biochemical marker in a sample of body fluid from a diseased patient, and the absence of a "normal" binding protein or biochemical marker characteristically found in samples from normal subjects. The method provides a reliable, accurate, safe and effective method to detect disease-specific biochemical markers for neurological syndromes., Diagnosis of Alzheimer's disease comprises (a) contacting in the presence of micromolar levels of Mn cerebrospinal fluid contg. a nucleotide binding protein with a mol. wt. of 43kd, where the protein is glutamine synthetase, with labelled ATP-GTP-analog photoaffinity, binding reagents; (b) fractionating the sample to

separate

photoaffinity-l labelled protein; (c) detecting the presence of sepd. protein, and (d) correlating the presence of the protein to the presence of Alzheimer's disease. Reagent is e.g. 32-P-8-azidoadenosine-5'-triphosphate. Sepn. is pref. performed by gel electrophoresis., USE/ADVANTAGE - Diagnosis of Alzheimer's disease and other neurological syndromes or diseases eg. ALs. Method is reliable, accurate, safe and effective.

L7: Entry 36 of 44

File: DWPI

Feb 19, 1998

DERWENT-ACC-NO: 1995-170233

DERWENT-WEEK: 199824

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TITLE: Aiding the diagnosis of Alzheimer's disease - comprises detecting a disease-specific biochemical marker macromolecule within a cerebro-spinal fluid or serum sample

ABEQ:

Diagnosis of Alzheimer's disease comprises (a) contacting in the presence of micromolar levels of Mn cerebrospinal fluid contg. a nucleotide binding protein with a mol. wt. of 43kd, where the protein is glutamine synthetase, with labelled ATP-GTP-analog photoaffinity, binding reagents; (b) fractionating the sample to separate photoaffinity-l labelled protein; (c) detecting the presence of sepd. protein, and (d) correlating the presence of the protein to the presence of Alzheimer's disease. Reagent is e.g. 32-P-8-azidoadenosine-5'-triphosphate. Sepn. is pref. performed by gel electrophoresis.

37. Document ID: US 6040140 A, WO 9426930 A1

L7: Entry 37 of 44

File: DWPI

Mar 21, 2000

DERWENT-ACC-NO: 1995-006818

DERWENT-WEEK: 200021

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TITLE: New acute lymphocytic leukaemia gene prods. - used for the diagnosis and treatment of leukaemia(s), partic. acute lymphoblastic or nonlymphoblastic leukaemia

PRIORITY-DATA: 1993US-0062443 (May 14, 1993), 1991US-0805093 (December 11, 1991), 1992US-0888839 (May 27, 1992), 1992US-0971094 (October 30, 1992), 1996US-0545860 (March 7, 1996)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

US 6040140 A

March 21, 2000

N/A

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C12Q001/68

WO 9426930 A1

November 24, 1994

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C12Q001/68

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

US 6040140A

December 11, 1991

1991US-0805093

CIP of

US 6040140A

May 27, 1992

1992US-0888839

CIP of

US 6040140A

October 30, 1992

1992US-0971094

CIP of

US 6040140A

May 14, 1993

1993US-0062443

CIP of

US 6040140A

April 22, 1994

1994WO-US04496

N/A

US 6040140A

March 7, 1996

1996US-0545860

N/A

WO 9426930A1

April 22, 1994

1994WO-US04496

N/A

INT-CL (IPC): A61K 39/395; A61K 48/00; C07H 21/02; C07H 21/04; C07K 15/28; C12P 19/34; C12Q 1/68; G01N 33/53; G01N 33/574

IN: CANAANI, E, CROCE, C

AB: (A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc., USE - The prods. and

methods are used for the diagnosis and treatment of human leukaemias., (A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc., USE - The prods. and methods are used for the diagnosis and treatment of human leukaemias.

L7: Entry 37 of 44

File: DWPI

Mar 21, 2000

DERWENT-ACC-NO: 1995-006818

DERWENT-WEEK: 200021

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TITLE: New acute lymphocytic leukaemia gene prods. - used for the diagnosis and treatment of leukaemia(s), partic. acute lymphoblastic or nonlymphoblastic leukaemia

ABTX:

(A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc.

ABEQ:
 (A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc.

38. Document ID: US 5506120 A, WO 9206211 A, JP 04148694 A, EP 591524 A1, EP 591524 A4, JP 95108232 B2
 L7: Entry 38 of 44

File: DWPI

Apr 9, 1996

DERWENT-ACC-NO: 1992-150895
 DERWENT-WEEK: 199620
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TITLE: High yield prodn. of peptide(s) with physiological activity - by expressing fused protein in transformant microorganism having peptide linked to carrier via dipeptide, then cleaving with protease

PRIORITY-DATA: 1990JP-0271880 (October 9, 1990)

PATENT-FAMILY:
 PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5506120 A			
April 9, 1996	N/A	027	C12N015/62
WO 9206211 A			
April 16, 1992	J	053	N/A
JP 04148694 A			
May 21, 1992	N/A	023	C12P021/06
EP 591524 A1			
April 13, 1994			

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 591524 A4	August 3, 1994	N/A	030 C12P021/06
JP 95108232 B2	November 22, 1995	N/A	000 N/A
US 5506120A	February 25, 1991	1991WO-JP00239	019 C12P021/02
US 5506120A	June 5, 1992	1992US-0853754	Cont of
US 5506120A	May 16, 1994	1994US-0243082	Cont of
WO 9206211 A	February 25, 1991	1991WO-JP00239	N/A
JP04148694A	October 9, 1990	1990JP-0271880	N/A
EP 591524A1	February 25, 1991	1991EP-0904654	N/A
EP 591524A1	February 25, 1991	1991WO-JP00239	N/A
EP 591524A1		WO 9206211	Based on
EP 591524A4		1991EP-0904654	N/A
JP95108232B2	October 9, 1990	1990JP-0271880	N/A
JP95108232B2		JP 4148694	Based on
INT-CL (IPC): C07K 13/00; C12N 15/09; C12N 15/62; C12P 21/02; C12P 21/06; C12R 1/12; C12P 21/02; C12R 1/125; C12P 21/02; C12R 1/125; C12P 21/02; C12R 1/125			
IN: YAMAMOTO, H, YAMASHITA, K, KUWATA, M			
AB: Peptides and proteins are obtd. by (a) producing a fused protein consisting of the desired peptide or protein linked to a carrier molecule by an enzymically-cleavable dipeptide; (b) cleaving the dipeptide by means of a protease (which may be an aminopeptidase or carboxypeptidase) to give the free desired protein or peptide. In (a) the fused protein is obtd. as the prod. of culture of a transformant microorganism and has			

the structure

A-B-C or C-B-A (where A is the carrier, B the dipeptide and C the desired peptide or protein; B is -X1-X2- where X1 is LYS, PRO, or ARG and X2 is LYS or ARG (but excepting X1=PRO, X2=ARG) or may have a multiple structure A-(B-C)n or (C-B)n-A (where n is pref.

2-20)., The carrier A is A pref. alpha-amylase, neutral protease, alkali protease,

cellulose, beta-lactamase, beta-galactosidase, chloroamphenicol acetyltransferase, RecA,

TrpE or human interferon 2 etc. The linker dipeptide is -LYS-ARG or -ARG-ARG-. The protease

in (b) is IRCM serine protease, I, POMC converting enzyme, or a protease derived from

Saccharomyces, Kluyveromyces, Sporobolomyces, Filobasidium, Hansenula, Issatchenkia, Pichia,

Rhodosporidium or Saccharomycopsis., USE/ADVANTAGE - High yield prodn. of peptides such as

insulin, gastrin, opioid peptides, epidermal growth factor, endoserine, vasoactive

intestinal peptide (VIP) substance P, calcitonin, insulin-dependent growth factor (I or II),

gramine, motilin, vasopressin, hirudin, egurin C, serum protease inhibitor, human albumin,

clotting factors or lymphokines., A new method of producing a peptide or a protein, wherein

said method comprises expressing a recombinant DNA in a host microorganism, said DNA

encoding a fusion protein represented by the formula A-B-C(I) or C-B-A(II) where A

represents a carrier, B represents an enzymatically excisable dipeptide of the formula X1-X2

(in which X1 is Lys, Arg or Pro bound to the C-terminus of A in the case of (I) and to the

C-terminus of C in the case of (II), and X2 is Lys or Arg bound to the N-terminus of C in

the case of (I) and to the N-terminus of A in the case of (II) provided that when X1 is Pro,

X2 is Arg, which does not occur in a desired peptide or protein, and C represents the

desired peptide or protein, said host microorganism being a mutant strain showing low

protease productivity derived from a parent Bacillus subtilis strain by introduction of a

spoOA-delta677 mutant gene, wherein said parent Bacillus subtilis lacks an ability to

produce either alkaline protease or neutral protease and shows a protease activity of not

more than about 3% as compared to wild strains, and treating said fusion protein at least

with a protease capable of specifically recognizing said dipeptide represented by B and

specifically hydrolyzing a peptide bond of said dipeptide.

L7: Entry 38 of 44

File: DWPI

Apr 9, 1996

DERWENT-ACC-NO: 1992-150895

DERWENT-WEEK: 199620

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TITLE: High yield prodn. of peptide(s) with physiological activity - by

expressing fused protein

in transformant microorganism having peptide linked to carrier via dipeptide, then cleaving with

protease

ABEQ:

A new method of producing a peptide or a protein, wherein said method comprises expressing a

recombinant DNA in a host microorganism, said DNA encoding a fusion protein represented by the

formula A-B-C(I) or C-B-A(II) where A represents a carrier, B represents an enzymatically

excisable dipeptide of the formula X1-X2 (in which X1 is Lys, Arg or Pro bound to the C-terminus

of A in the case of (I) and to the C-terminus of C in the case of (II), and X2 is Lys or Arg

bound to the N-terminus of C in the case of (I) and to the N-terminus of A in the case of (II)

provided that when X1 is Pro, X2 is Arg, which does not occur in a desired peptide or protein,

and C represents the desired peptide or protein, said host microorganism being a mutant strain

showing low protease productivity derived from a parent Bacillus subtilis strain by introduction

of a spoOA-delta677 mutant gene, wherein said parent Bacillus subtilis lacks an ability to

produce either alkaline protease or neutral protease and shows a protease activity of not more

than about 3% as compared to wild strains, and treating said fusion protein at least with a

protease capable of specifically recognizing said dipeptide represented by B and specifically

hydrolyzing a peptide bond of said dipeptide.

39. Document ID: WO 9101006 A, CA 2018856 A, JP 04500731 W, EP 617790 A1, US 5364796 A, EP 617790 B1, DE 69023517 E, ES 2081993 T3, JP 2574068 B2

L7: Entry 39 of 44

File: DWPI

Jan 24, 1991

DERWENT-ACC-NO: 1991-051402

DERWENT-WEEK: 199810

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TITLE: Multilayer diagnostic assay system - esp. useful for estimating sites on thyroxine binding globulin (TBG) not occupied by thyroxine

PRIORITY-DATA: 1989US-0378062 (July 11, 1989)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

WO 9101006 A

January 24, 1991

N/A

020

N/A

CA 2018856 A

January 11, 1991

N/A

000

N/A

JP 04500731 W

February 6, 1992

N/A

006

N/A

EP 617790 A1

October 5, 1994

E

020

G01N033/68

US 5364796 A

November 15, 1994

N/A

006

G01N033/53

EP 617790 B1

November 8, 1995
E
010
G01N033/68
DE 69023517 E
December 14, 1995
N/A
000
G01N033/68
ES 2081993 T3
March 16, 1996
N/A
000
G01N033/68
JP 2574068 B2
January 22, 1997
N/A
005
G01N033/543

APPLICATION-DATA:
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
JP04500731W June 12, 1990	1990JP-0509877	N/A
EP 617790A1 June 12, 1990	1990EP-0909892	N/A
EP 617790A1 June 12, 1990	1990WO-US03313	N/A
EP 617790A1	WO 9101006	Based on
US 5364796A July 11, 1989	1989US-0378062	N/A
EP 617790B1 June 12, 1990	1990EP-0909892	N/A
EP 617790B1 June 12, 1990	1990WO-US03313	N/A
EP 617790B1	WO 9101006	Based on
DE69023517E June 12, 1990	1990DE-0623517	N/A
DE69023517E June 12, 1990	1990EP-0909892	N/A
DE69023517E June 12, 1990	1990WO-US03313	N/A
DE69023517E	EP 617790	Based on
DE69023517E	WO 9101006	Based on
ES 2081993T3 June 12, 1990	1990EP-0909892	N/A

ES 2081993T3
EP 617790
Based on
JP 2574068B2
June 12, 1990
1990JP-0509877
N/A
JP 2574068B2
June 12, 1990
1990WO-US03313
N/A
JP 2574068B2
JP 4500731
Previous Publ.
JP 2574068B2
WO 9101006
Based on

INT-CL (IPC): G01N 21/00; G01N 21/78; G01N 33/53; G01N 33/533; G01N 33/543; G01N 33/563; G01N 33/58; G01N 33/68; G01N 33/78

IN: BLACKWOOD, J J, INBAR, S, PATZKE, J V

AB: Method for assessing the available ligand binding sites on proteins comprises (a) distributing a sample of a fluid containing a protein (I) across the surface of a multilayer diagnostic assay element comprising (i) a light-blocking layer which is permeable to the fluid but impermeable to (I); and (ii) a reagent layer comprising a ligand (II), which can bind to available binding sites on (I); (b) measuring the amount of (II) which is in the reagent layer or on (I); and (c) assessing the available ligand binding sites on (I) as a function of the amount of (II) in the reagent layer or on (I)., USE - Assay may be used to assess the available binding sites on receptors for hormones, on proteins eg folic binding proteins for folic acid, or for assessing the presence of available binding sites on endogenous antibodies which are raised against infectious diseases. The assay system is preferred (as claimed) to provide an indirect estimate of the binding sites on TBG which are not occupied by thyroid hormones. This result, taken together with that obtained in a separate assay for total T4 carried out with another sample of the same fluid, provides an indirect measure of free T4 in the sample and can be used to calculate a free thyroxine index (FTI)., A method for assessing the available ligand binding sites on proteins comprising (a) distributing a sample of a fluid containing a protein across the surface of a multilayer diagnostic assay element which comprises: (i) a light blocking layer which is permeable to said fluid but impermeable to said protein; and (ii) a reagent layer comprising a ligand which is capable of binding to available binding sites on said protein; (b) measuring the amount of ligand which is present in said reagent layer on or said protein; and (c) assessing the available ligand binding sites on said protein as a function of the amount of ligand present in said reagent layer or on said protein., Assessing the available ligand binding sites on proteins comprises (a) distributing a sample of a fluid containing a protein across the surface of a multilayer diagnostic assay element comprising (i) a light blocking layer which is permeable to the fluid but impermeable to the protein, and (ii) a reagent layer comprising a ligand which binds to available binding sites on the protein, (b) measuring the amount of ligand in the reagent layer or on the protein, and (c)

assessing the
 available ligand binding sites on the protein as a function of the amt. of
 ligand in the
 reagent layer or on the protein., Pref. the ligand is bound to a label
 comprising a
 fluorescent gp. The ligand is thyroxine or triiodothyronine., USE - Used
 for assessing
 available binding sites on proteins in biological fluids, e.g. thyroxine
 binding proteins in
 serum or plasma samples.

L7: Entry 39 of 44

File: DWPI

Jan 24, 1991

DERWENT-ACC-NO: 1991-051402
 DERWENT-WEEK: 199810
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TITLE: Multilayer diagnostic assay system - esp. useful for estimating sites
 on thyroxine binding
 globulin (TBG) not occupied by thyroxine

ABEQ:
 A method for assessing the available ligand binding sites on proteins
 comprising (a) distributing
 a sample of a fluid containing a protein across the surface of a multilayer
 diagnostic assay
 element which comprises: (i) a light blocking layer which is permeable to
 said fluid but
 impermeable to said protein; and (ii) a reagent layer comprising a ligand
 which is capable of
 binding to available binding sites on said protein; (b) measuring the amount
 of ligand which is
 present in said reagent layer on or said protein; and (c) assessing the
 available ligand binding
 sites on said protein as a function of the amount of ligand present in said
 reagent layer or on
 said protein.

ABEQ:
 Assessing the available ligand binding sites on proteins comprises (a)
 distributing a sample of a
 fluid contg. a protein across the surface of a multilayer diagnostic assay
 element comprising (i)
 a light blocking layer which is permeable to the fluid but impermeable to
 the protein, and (ii) a
 reagent layer comprising a ligand which binds to available binding sites on
 the protein, (b)
 measuring the amt. of ligand in the reagent layer or on the protein, and (c)
 assessing the
 available ligand binding sites on the protein as a function of the amt. of
 ligand in the reagent
 layer or on the protein.

40. Document ID: EP 406216 A, CA 2019745 C, NO 9002823 A, CA
 2019745 A, JP 03038528 A, FI 9003197 A, US
 5143901 A, EP 406216 B1, US 5254532 A, DE 59003060 G, ES 2061007
 T3, FI 94927 B, AT 8901551 A, AT 402153 B
 L7: Entry 40 of 44

File: DWPI

Jan 2, 1991

DERWENT-ACC-NO: 1991-009510
 DERWENT-WEEK: 199712
 COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Protein S-contg. pharmaceutical prepn. - having 50 times more
 protein S than native plasma

and useful in prevention of thrombosis

PRIORITY-DATA: 1989AT-0001551 (June 26, 1989)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

EP 406216 A	January 2, 1991	N/A	000	N/A
CA 2019745 C	December 31, 1996	N/A	000	A61K038/48
NO 9002823 A	December 27, 1990	N/A	000	N/A
CA 2019745 A	December 26, 1990	N/A	000	N/A
JP 03038528 A	February 19, 1991	N/A	000	N/A
FI 9003197 A	December 27, 1990	N/A	000	N/A
US 5143901 A	September 1, 1992	N/A	005	A61K037/00
EP 406216 B1	October 13, 1993	G	008	C07K003/20
US 5254532 A	October 19, 1993	N/A	005	A61K037/00
DE 59003060 G	November 18, 1993	N/A	000	C07K003/20
ES 2061007 T3	December 1, 1994	N/A	000	C07K003/20
FI 94927 B	August 15, 1995	N/A	000	A61K038/17
AT 8901551 A	July 15, 1996	N/A	000	A61K038/36
AT 402153 B	January 15, 1997	N/A		

000

A61K038/36

A61K 38/36; A61K 38/48; C07K 1/22; C07K 3/20

IN: LINNAU, Y, MOLINARI, E, PFEILER, S, SCHWARZ, H P

APPLICATION-DATA:
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
EP 406216A June 18, 1990	1990EP-0890184 N/A	
CA 2019745C June 25, 1990	1990CA-2019745 N/A	
JP03038528A June 25, 1990	1990JP-0166528 N/A	
US 5143901A June 19, 1990	1990US-0540357 N/A	
EP 406216B1 June 18, 1990	1990EP-0890184 N/A	
US 5254532A June 19, 1990	1990US-0540357 Cont of	
US 5254532A February 21, 1992	1992US-0840719 N/A	
US 5254532A	US 5143901 Cont of	
DE59003060G June 18, 1990	1990DE-0503060 N/A	
DE59003060G June 18, 1990	1990EP-0890184 N/A	
DE59003060G	EP 406216 Based on	
ES 2061007T3 June 18, 1990	1990EP-0890184 N/A	
ES 2061007T3	EP 406216 Based on	
FI 94927B June 26, 1990	1990FI-0003197 N/A	
FI 94927B	FI 9003197 Previous Publ.	
AT 8901551A June 26, 1989	1989AT-0001551 N/A	
AT 402153B June 26, 1989	1989AT-0001551 N/A	
AT 402153B	AT 8901551 Previous Publ.	

INT-CL (IPC): A61K 35/16; A61K 37/00; A61K 37/02; A61K 38/17;

AB: Compsn. for treating or preventing thrombosis or thromboembolic complications has a content of protein S at least 50 times that of native plasma and is free of C4b-binding protein. Opt. it also contains activated protein C., USE/ADVANTAGE - The compsns. are used;

(1) to prevent thromboembolic complications in patients with inherited or acquired protein S deficiency; (2) to treat patients with elevated levels of C4b-binding protein or (3), opt. combined with protein C, for immobilisation on the surfaces of vascular prosthesis to inhibit thrombus formation. Highly purified and conc. protein S used in the compsn. contain none of the activity-inhibiting components not orally present in plasma. (Previously notified in Week 9102), A preparation for treating and preventing thromboses and thromboembolic complications, containing human plasma protein S at a concentration of at least 1.25 mg protein S/ml and free of C4-binding protein, if desired, in combination with a content of activated protein C., Pharmaceutical compsn. comprises purified protein-S, immobilised on artificial vein surfaces. Process for preventing thrombosis comprises administration of purified protein-S (at least 50 times that in natural plasma), and opt. activated protein-C, immobilised on artificial vein surfaces. Protein-S is purified by polyclonal and monoclonal antibody affinity chromatography, and is not contaminated with C4-binding protein., USE - The prods. are therapeutics and prophylactics for thrombotic and thromboembolic conditions., Process for the prophylaxis and therapy of thromboembolic complications in patients with congenital or acquired protein-S deficiency comprises admin. of a compsn. contg. protein-S (at least 50 times the concn. normally present in natural plasma), and pref. also activated protein-C, dispersed with the usual pharmaceutical carriers and opt. additives. The protein-S is previously purified from C4-b binding protein contaminant by polyclonal or monoclonal affinity chromatography., USE - The prods. are valuable anti-thrombotic agents avoiding haemorrhages as side effects.

L7: Entry 40 of 44

File: DWPI

Jan 2, 1991

DERWENT-ACC-NO: 1991-009510

DERWENT-WEEK: 199712

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TITLE: Protein S-contg. pharmaceutical prepn. - having 50 times more protein S than native plasma and useful in prevention of thrombosis

ABTX:

USE/ADVANTAGE - The compsns. are used; (1) to prevent thromboembolic complications in patients with inherited or acquired protein S deficiency; (2) to treat patients with elevated levels of C4b-binding protein or (3), opt. combined with protein C, for immobilisation on the surfaces of vascular prosthesis to inhibit thrombus formation. Highly purified and conc. protein S used in the compsn. contain none of the activity-inhibiting components not orally present in plasma.

(Previously notified in Week 9102)

ABEQ:

A preparation for treating and preventing thromboses and thromboembolic complications, containing human plasma protein S at a concentration of at least 1.25 mg protein S/ml and free of C4-binding protein, if desired, in combination with a content of activated protein C.

41. Document ID: EP 356836 A, DE 68915226 E, EP 356836 B1, ES 2056164 T3, JP 03086900 A, JP 95020997 B2, US 5043425 A

L7: Entry 41 of 44

File: DWPI

Mar 7, 1990

DERWENT-ACC-NO: 1990-068657

DERWENT-WEEK: 199010

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TITLE: New thrombin-binding substances - capable of promoting thrombin catalysed activation of protein C and prolonging clotting time, used to treat thrombosis

PRIORITY-DATA: 1989JP-0202027 (August 3, 1989), 1988JP-0214139 (August 29, 1988), 1989JP-0116471 (May 10, 1989)

PATENT-FAMILY:

PUB-NO

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 356836 A	March 7, 1990	G	013	N/A
DE 68915226 E	June 16, 1994	N/A	000	A61K035/22
EP 356836 B1	May 11, 1994	E	016	A61K035/22
ES 2056164 T3	October 1, 1994	N/A	000	A61K035/22
JP 03086900 A	April 11, 1991	N/A	000	N/A
JP 95020997 B2	March 8, 1995	N/A	006	C07K014/47
US 5043425 A	August 27, 1991	N/A	000	N/A

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

EP 356836A	August 18, 1989	1989EP-0115272	N/A
DE68915226E	August 18, 1989	1989DE-0615226	N/A
DE68915226E	August 18, 1989	1989EP-0115272	N/A
DE68915226E		EP 356836	Based on
EP 356836B1	August 18, 1989	1989EP-0115272	N/A
ES 2056164T3	August 18, 1989	1989EP-0115272	N/A
ES 2056164T3		EP 356836	Based on
JP03086900A	August 3, 1989	1989JP-0202027	N/A
JP95020997B2	August 3, 1989	1989JP-0202027	N/A
JP95020997B2		JP 3086900	Based on
US 5043425A	August 16, 1989	1989US-0394715	N/A

INT-CL (IPC): A61K 35/22; A61K 38/00; C07K 1/00; C07K 1/16; C07K 14/47; C12P 21/00; C12P 21/00; C12R 1/91

IN: AOKI, N, KIMURA, S, SHIRATSUCHI, M, SHIRATSUCHI, M

AB: Thrombin binding substances are claimed having the following characteristics:
(A) (a) mol. wt. % 90,000-92,000 under reducing conditions and 55,000-58,000 under non-reducing conditions; (b) isoelectric point: pH 6-6.8; (c) affinity: has strong affinity to thrombin, (d) activity: (i) capable of promoting the thrombin catalysed activation of protein C, (ii) prolongs clotting time and (e) stability: stable to denaturing agents (sodium dodecylsulphate and urea); (B) (a) mol. wt. 98,000-105,000 under reducing conditions and 60,000-65,000 under non-reducing conditions; (b) isoelectric point: pH 5.8-6.5; (c) affinity: strong affinity to thrombin; (d) activity: (i) capable of promoting the thrombin catalysed activation of protein C, (ii) prolongs clotting time and (e) stability: stable to denaturing agents (sodium dodecylsulphate and urea).
USE/ADVANTAGE - Thrombin-binding substances are high mol. wt. substances with calcium-binding sites so show more natural pharmaceutical effect than thrombin-binding substances with smaller mol. wt. Used for treating thrombosis involving anticoagulation and fibrinolytic systems

which control blood coagulation., A thrombin-binding substance having the following characteristics: (a) molecular weight: 90,000-92,000 under reduced conditions 55,000-58,000 under unreduced conditions (b) isoelectric point: pH 6.0-6.8 (c) affinity: has strong affinity to thrombin (d) activity: (1) capable of promoting the thrombin catalysed activation of protein C (2) prolongs clotting time; and (e) stability: stable to denaturing agents (sodium dodecyl sulfate and urea)., A purified thrombin-binding substance having the following characteristics: (a) molecular weight as determined by SDS-PAGE: 90,000-92,000 under reduced conditions 55,000-58,000 under unreduced conditions (b) isoelectric point: pH 6.0-6.8 (c) affinity: has strong affinity to thrombin (d) activity: (1) capable of promoting the thrombin catalysed activation of protein C (2) prolongs clotting time; and (e) stability: stable to denaturing agents (sodium dodecylsulfate and urea) (f) amino acid composition: Aspartic acid 9.59, Threonine 4.45, Serine 5.42, Glutamic acid 11.29, Proline 8.86, Glycine 10.26, Alanine 10.88, 1/2 Cystine 8.27, Valine 5.54, Methionine 0.78, Isoleucine 2.84, Leucine 7.15, Tyrosine 2.25 and Phenylalanine 3.50., (-pp)

L7: Entry 41 of 44

File: DWPI

Mar 7, 1990

DERWENT-ACC-NO: 1990-068657

DERWENT-WEEK: 199010

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TITLE: New thrombin-binding substances - capable of promoting thrombin catalysed activation of protein C and prolonging clotting time, used to treat thrombosis

42. Document ID: EP 354504 A, AU 8939372 A, DK 8903887 A, FI 8903724 A, JP 02046296 A, NO 8903196 A, PT 91391 A

L7: Entry 42 of 44

File: DWPI

Feb 14, 1990

DERWENT-ACC-NO: 1990-046218

DERWENT-WEEK: 199007

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TITLE: Human protein C deriv. - having Gla domain replaced by the bovine Gla to increase calcium binding activity and improve activation

PRIORITY-DATA: 1988JP-0197144 (August 9, 1988)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

EP 354504 A

February 14, 1990

E

017

AU 8939372 A	April 12, 1990	N/A	
		N/A	000
DK 8903887 A	February 10, 1990	N/A	N/A
		N/A	000
FI 8903724 A	February 10, 1990	N/A	N/A
		N/A	000
JP 02046296 A	February 15, 1990	N/A	N/A
		N/A	000
NO 8903196 A	March 5, 1990	N/A	N/A
		N/A	000
PT 91391 A	March 8, 1990	N/A	N/A
		N/A	000
			N/A

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

EP 354504A

August 5, 1989

1989EP-0114505

N/A

JP02046296A

August 9, 1988

1988JP-0197144

N/A

INT-CL (IPC): A61K 37/54; C07H 21/04; C07K 13/00; C07K 15/06; C12N 5/00; C12N 9/64; C12N 15/57; C12P 19/00; C12P 21/02

IN: HASHIMOTO, T, TAKAHASHI, M

AB: (A) A deriv. of human protein C is claimed characterised in that its amino terminal region having gamma-carboxylated glutamic acid residues (Gla domain) is replaced by the Gla domain of bovine protein C or by an equivalent of this bovine protein sequence with respect to its calcium binding activity and/or its enhanced protein C activity. (B) also claimed are DNA coding for the protein of (A), a gene structure contg. the DNA and a host cell contg. the gene structure., USE/ADVANTAGE - The hybrid proteins have an increased number of glutamic residues (from 9 to 11). Through th increase of the number of gamma-carboxylation sites, enhanced calcium binding activity of protein C and improved activation of protein C, is obt'd. The activated protein C inhibits blood coagulation or accelerates blood fibrinolysis and is used for treating blood coagulation.

L7: Entry 42 of 44

File: DWPI

Feb 14, 1990

DERWENT-ACC-NO: 1990-046218
DERWENT-WEEK: 199007
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Human protein C deriv. - having Gla domain replaced by the bovine Gla to increase calcium binding activity and improve activation

ABTX:

USE/ADVANTAGE - The hybrid proteins have an increased number of glutamic residues (from 9 to 11).

Through the increase of the number of gamma-carboxylation sites, enhanced calcium binding activity of protein C and improved activation of protein C, is obtd. The activated protein C inhibits blood coagulation or accelerates blood fibrinolysis and is used for treating blood coagulation.

43. Document ID: EP 253331 A, DE 3750664 G, EP 253331 B1, ES 2065318 T3, JP 63030423 A, JP 63146898 A, US 5047503 A

L7: Entry 43 of 44

File: DWPI

Jan 20, 1988

DERWENT-ACC-NO: 1988-015706
DERWENT-WEEK: 198803
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TITLE: Two new thrombin binding proteins from human urine - promoting activation of protein C and useful in treatment of thrombosis

PRIORITY-DATA: 1986JP-0172626 (July 22, 1986), 1986JP-0166084 (July 15, 1986), 1987JP-0168428 (July 6, 1987)

PATENT-FAMILY:
PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 253331 A			
January 20, 1988	E	027	N/A
DE 3750664 G			
November 24, 1994	N/A	000	C07K015/06
EP 253331 B1			
October 19, 1994	E	009	C07K015/06
ES 2065318 T3			
February 16, 1995	N/A	000	C07K015/06
JP 63030423 A			
February 9, 1988	N/A	000	N/A
JP 63146898 A			
June 18, 1988			

N/A

000

N/A

US 5047503 A

September 10, 1991

N/A

000

N/A

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

EP 253331 A

July 10, 1987

1987EP-0110005

N/A

DE 3750664 G

July 10, 1987

1987DE-3750664

N/A

DE 3750664 G

July 10, 1987

1987EP-0110005

N/A

DE 3750664 G

EP 253331

Based on

EP 253331 B1

July 10, 1987

1987EP-0110005

N/A

ES 2065318 T3

July 10, 1987

1987EP-0110005

N/A

ES 2065318 T3

EP 253331

Based on

JP63030423 A

July 22, 1986

1986JP-0172626

N/A

JP63146898 A

July 6, 1987

1987JP-0168428

N/A

US 5047503 A

July 10, 1987

1987US-0072051

N/A

INT-CL (IPC): A61K 35/22; C07K 3/12; C07K 15/06; C12N 5/00; C12N 15/00; C12P 21/00

IN: AOKI, N, KIMURA, S, SHIRATSUCHI, M, KLMURA, S, SHIRATSUCH, M

AB: Two new thrombin-binding substances, (I) and (II), derived from human urine have the following characteristics: (I) mol. wt., for (I) 40500-52500 and 29000-49000 by Na dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE) under reducing and non-reducing conditions, respectively: for (II) 32000-48000 and 21000-41000; (2) isoelectric point: for (I) 5-5.3, for (II) 4.9-5.7; (3) for both cpds., strong affinity to thrombin; promotion of thrombin-catalysed activated of protein C; prolongation of clotting time and stability towards denaturing agents such as urea and SDS., USE/ADVANTAGE - (I) and (II) act as fibrinolytic accelerators or anticoagulants, so are useful for treating thrombosis and similar conditions. They are prepd. more easily than known placental

thrombin-binding substances, and can be isolated from urine after recovery of other useful prods. such as urokinase., A process for preparing a thrombin-binding substance having the following characteristics: (a) molecular weight: 40,000 +/- 8,000 in reduced condition by SDS PAGE 31,000 +/- 10,000 in unreduced condition by SDS PAGE (b) isoelectric point: pH 4.9-5.7 (c) affinity: strong affinity to thrombin (d) activity: (1) capable of promoting the thrombin catalysed activation of protein C (2) prolongs clotting time; and (e) stability; stable to denaturing agents (urea and sodium dodecylsulfate), which comprises fractionating human urine by ion-exchange chromatography, affinity chromatography using a thrombin-bound carrier, immune adsorption column chromatography, gel filtration, and/or molecular-weight fractionation., A new thrombin-binding substance is prepd. by successively subjecting human urine to ion exchange chromatography, affinity chromatography on a column of a thrombin-bound carrier, gel-filtration and molecular wt. fractionation. Pref. benzamidine HCl or aprotinin is added to the urine before ion exchange chromatography. The urine may be subjected to immune adsorption column chromatography using as packing a monoclonal antibody specific to the thrombin-binding substance bound on an insol. carrier, followed by ion exchange. Two thrombin-binding substances are obtd. (a) with MW 46500 +/- 6000 in reduced condition by SDS PAGE and 39000 +/- 10000 in unreduced condition; isoelectric pt. pH 5.0-5.3; strong affinity to thrombin; stable to denaturing agents (urea or Na dodecylsulphate). (b) has MW 40000 +/- 8000 in reduced condition and 31000 +/- 10000 in unreduced condition; isoelectric pt. pH 4.9-5.7; and other characteristics as (a). USE - Both cpds. are capable of promoting the thrombin-catalysed activation of protein C and prolonging clotting time. They are also fibrinolytic accelerators and anticoagulants used to control coagulation of blood., (7pp)

L7: Entry 43 of 44

File: DWPI

Jan 20, 1988

DERWENT-ACC-NO: 1988-015706
DERWENT-WEEK: 198803
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TITLE: Two new thrombin binding proteins from human urine - promoting activation of protein C and useful in treatment of thrombosis< /td>

44. Document ID: EP 155852 A, DE 3577399 G, EP 155852 B, JP 60199819 A, JP 93045600 B, US 4638050 A
L7: Entry 44 of 44

File: DWPI

Sep 25, 1985

DERWENT-ACC-NO: 1985-238346
DERWENT-WEEK: 198539
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TITLE: Thrombin binding substance - obtd. from human placenta used as thrombolytic or anticoagulant

PRIORITY-DATA: 1984JP-0055792 (March 23, 1984)

PATENT-FAMILY:
PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 155852 A	September 25, 1985	E	016
DE 3577399 G	June 7, 1990	N/A	N/A
EP 155852 B	May 2, 1990	N/A	000
JP 60199819 A	October 9, 1985	N/A	N/A
JP 93045600 B	July 9, 1993	N/A	000
US 4638050 A	January 20, 1987	N/A	005

APPLICATION-DATA:
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
EP 155852A	March 21, 1985	1985EP-0301959
JP60199819A	March 23, 1984	1984JP-0055792
JP93045600B	March 23, 1984	1984JP-0055792
JP93045600B		JP60199819
US 4638050A	March 20, 1985	1985US-0713821

INT-CL (IPC): A61K 35/50; A61K 37/04; C07K 3/02; C07K 15/06

IN: AOKI, N, KUROSAWA, S

AB: A thrombin-binding substance (I) derived from human tissue has the following props. (a) mol.wt. 88,000+/-20,000 in the reduced condition and 71,000+/-20,000 in the

unreduced condition, (c) isoelectric point pH 4.2+/-0.5, (c) affinity:strong for thrombin, (d) capable of promoting the thrombin-catalysed activation of protein C and prolonging clotting time and (e) stability:stable over a pH range of 2-10 and stable to denaturing agents (sodium dodecylsulphate and urea) and to a pepsin treatment., USE - (I) is useful as a thrombolytic agent or an anticoagulating agent., A thrombin-binding substance effective when bonded with thrombin to enhance the activation of protein C, derived from human tissue and having the following characteristics: (a) molecular wt.; 88,000 +/- 20,000 in the reduced condition and 71,000 +/- 20,000 in the unreduced condition; (b) isoelectric point; pH 4.2 +/- 0.5; (c) affinity; strong for thrombin; (d) activities; capable of promoting the thrombin-catalysed activation of protein C and prolonging clotting time; and (e) stability; stable over a pH range of 2-10 and stable to denaturing agents (dodecylsulphate and urea) and to a pepsine treatment. (8pp), Thrombin binding substance (TBS) is obtd. by (a) extracting human tissue, esp. the placenta, with a buffer contg. a nonionic surfactant and (b) isolating the pure TBS from the extract by diisopropylphosphorothrombin affinity chromatography and/or gel filtration and pref. (c) eluting the TBS with a buffer contg. NaCl, EDTA, benzamidine HCl and a nonionic surfactant., The TBS (a) has a mol.wt. 68,000-108,000 in reduced form and 51,000-91,000 in unreduced form, (b) has an isoelectric point pH 3.7-4.7, (c) has a strong affinity for thrombin, (d) is able to prevent the thrombin catalysed activation of protein C and prolongs clotting time and (e) is stable at pH 2-10, stable to denaturing agents and pepsin treatment., USE/ADVANTAGE - As thrombolytic agent or anticoagulating agent; the agent can be obtd. in pure form. B(6pp)

L7: Entry 44 of 44

File: DWPI

Sep 25, 1985

DERWENT-ACC-NO: 1985-238346
DERWENT-WEEK: 198539
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Thrombin binding substance - obtd. from human placenta used as thrombolytic or anticoagulant

ABEQ:

A thrombin-binding substance effective when bonded with thrombin to enhance the activation of protein C, derived from human tissue and having the following characteristics: (a) molecular wt.; 88,000 +/- 20,000 in the reduced condition and 71,000 +/- 20,000 in the unreduced condition; (b) isoelectric point; pH 4.2 +/- 0.5; (c) affinity; strong for thrombin; (d) activities; capable of promoting the thrombin-catalysed activation of protein C and prolonging clotting time; and (e) stability; stable over a pH range of 2-10 and stable to denaturing agents (dodecylsulphate and urea) and to a pepsine treatment. (8pp)

09/139425
A11#14

Set Items Description

? s protein(w)c

2938916 PROTEIN
2178289 C
S1 27187 PROTEIN(W)C
? s epcr

S2 96 EPCR
? s s1(w)receptor

27187 S1
1321224 RECEPTOR
S3 134 S1(W)RECEPTOR
? s s2 or s3

96 S2
134 S3
S4 147 S2 OR S3
? s antibod?

Processing
S5 1478948 ANTIBOD?
? s treat? or diagnos?

Processing
Processing
4385448 TREAT?
3971290 DIAGNOS?
S6 7599752 TREAT? OR DIAGNOS?
? s s4 and s5

147 S4
1478948 S5
S7 26 S4 AND S5
? s s1 and s5

27187 S1
1478948 S5
S8 3969 S1 AND S5
? s bind? or bound

1571243 BIND?
401937 BOUND
S9 1759385 BIND? OR BOUND
? rd

>>>A maximum of 5000 items can be processed.
<-----User Break----->
!

? ds

Set Items Description
S1 27187 PROTEIN(W)C
S2 96 EPCR
S3 134 S1(W)RECEPTOR
S4 147 S2 OR S3
S5 1478948 ANTIBOD?
S6 7599752 TREAT? OR DIAGNOS?
S7 26 S4 AND S5
S8 3969 S1 AND S5
S9 1759385 BIND? OR BOUND
? s s1(n5)s9

27187 S1
1759385 S9
S10 2429 S1(N5)S9
? s s10 and s6

2429 S10
7599752 S6
S11 423 S10 AND S6
? s s4 and s9

147 S4
1759385 S9
S12 76 S4 AND S9
? s s7 or s12

26 S7
76 S12
S13 78 S7 OR S12
? rd

...examined 50 records (50)
...completed examining records
S14 39 RD (unique items)
? s s14 and py<1998

Processing
Processing
39 S14
28044798 PY<1998
S15 14 S14 AND PY<1998
? t s15/3,ab/1-14

15/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11279552 BIOSIS NO.: 199800060884
Specific %%%binding%% of activated protein C (APC) to vascular smooth muscle cells is not due to the endothelial receptor (%%EPCR%%).
AUTHOR: O'Regan D J(a); Brennard D(a); Esmon C T; Goodwin C A(a); Kakkar V
V(a); Scully M F(a)
AUTHOR ADDRESS: (a)Thrombosis Res. Inst., Emmanuel Kaye Build., Manresa Rd., London SW3 6LR**UK
JOURNAL: Blood 90 (10 SUPPL. 1 PART 2):p78B-79B Nov. 15, %%%1997%%
CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997

15/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11174614 BIOSIS NO.: 199799795759
The interaction between the endothelial cell %%%protein%% %%%C%% %%%receptor%% and protein C is dictated by the gamma-carboxyglutamic acid domain of protein C.
AUTHOR: Regan Lisa M; Mollica Jeffery S; Rezaie Alireza R; Esmon Charles T
(a)
AUTHOR ADDRESS: (a)Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Foundation, 825 N. E. 13th St., Oklahoma City**USA
JOURNAL: Journal of Biological Chemistry 272 (42):p26279-26284 %%%1997%%
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %%%protein%% %%%C%% %%%receptor%% (%%%EPCR%%) %%%binds%% to both protein C and activated protein C (APC) with similar affinity. Removal of the Gla domain of protein C results in the loss of most of the %%%binding%% affinity. This observation is compatible with at least two models: 1) the Gla domain of protein C interacts with phospholipid on cell surfaces to stabilize interaction

with %EPCR% or 2) the Gla domain of protein C makes specific protein-protein interactions with %EPCR%. The latter model predicts that chimeric proteins containing the protein C Gla domain should interact with %EPCR%. To test this, we constructed a prothrombin chimera in which the Gla domain and aromatic stack of prothrombin were replaced with the corresponding region of protein C. The 125I-labeled chimera (K-d = 176 nM) and 125I-APC (K-d = 65 nM) both %bound% specifically to 293 cells stably transfected with %EPCR%, but both %bound% poorly to sham-transfected cells. The chimera also blocked APC %binding% to %EPCR%-transfected cells in a dose-dependent fashion (K-i approx 139 nM) similarly to protein C (K-i approx 75 nM). Chimera %binding% to %EPCR%-transfected cells was blocked by soluble %EPCR%, demonstrating direct protein-protein interaction between the chimera and %EPCR%. Consistent with this conclusion, the isolated Gla domain of protein C-blocked APC %binding% to %EPCR%-transfected cells (IC-50 = 2 μ M). No inhibition was observed with the isolated prothrombin Gla domain. A protein C chimera with the prothrombin Gla domain and aromatic stack failed to %bind% to %EPCR% detectably. These data suggest that the Gla domain of protein C is responsible for much of the %binding% energy and specificity of the protein C-%EPCR% interaction.

%1997%

15/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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11064593 BIOSIS NO.: 199799685738
Identification of functional endothelial %protein% %C% %receptor% in human plasma.
AUTHOR: Kurosawa Shinichiro; Stearns-Kurosawa Deborah J; Hidari Noriko; Esmen Charles T(a)
AUTHOR ADDRESS: (a)825 N.E. 13th St., Oklahoma City, OK 73104**USA
JOURNAL: Journal of Clinical Investigation 100 (2):p411-418
%1997%
ISSN: 0021-9738
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %protein% %C% %receptor% (%EPCR%) %binds% protein C and facilitates activation by the thrombin-thrombomodulin complex. %EPCR% also %binds% activated protein C (APC) and inhibits APC anticoagulant activity. In this study, we detected a soluble form of %EPCR% in normal human plasma. Plasma %EPCR% appears to be approx 43,000 D, and circulates at approx 100 ng/ml (98.4 \pm 27.8 ng/ml, n = 22). Plasma %EPCR% was purified from human citrated plasma using ion exchange, immunoaffinity, and protein C affinity chromatography. Flow cytometry experiments demonstrated that plasma %EPCR% %bound% APC with an affinity similar to that previously determined for recombinant soluble %EPCR% (K-dapp = 30 nM). Furthermore, plasma %EPCR% inhibited both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage Factor Xa clotting assay. The physiological function of plasma %EPCR% is uncertain, but if the local concentrations are sufficiently high, particularly in disease states, the present data suggest that the soluble

plasma %EPCR% could attenuate the membrane-%bound% %EPCR% augmentation of protein C activation and the anticoagulant function of APC.

%1997%

15/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10684157 BIOSIS NO.: 199799305302
The endothelial cell %protein% %C% %receptor% participates in protein C activation.
AUTHOR: Kurosawa Shinichiro(a); Fukudome Kenji; Stearns-Kurosawa Debbie; Mollica Jeff; Ferrell Gary; Hidari Noriko; Esmen Charles T
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Fdn., Oklahoma City, OK**USA
JOURNAL: Circulation 94 (8 SUPPL.):p1694 %1996%
CONFERENCE/MEETING: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1996

15/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10574195 BIOSIS NO.: 199699195340
The endothelial cell %protein% %C% %receptor% augments protein C activation by the thrombin-thrombomodulin complex.
AUTHOR: Stearns-Kurosawa Deborah J; Kurosawa Shinichiro; Mollica Jeffery S; Ferrell Gary L; Esmen Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst. Res. Lab., Acree-Woodworth Res. Building, 820 NE 15, Room A205, Oklahom**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (19):p10212-10216 %1996%
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein C activation on the surface of the endothelium is critical to the negative regulation of blood coagulation. We now demonstrate that monoclonal %antibodies% that block protein C %binding% to the endothelial cell %protein% %C% %receptor% (%EPCR%) reduce protein C activation rates by the thrombin-thrombomodulin complex on endothelium, but that %antibodies% that %bind% to %EPCR% without blocking protein C %binding% have no effect. The kinetic result of blocking the %EPCR%-protein C interaction is an increased apparent K-m for the activation without altering the affinity of thrombin for thrombomodulin. Activation rates of the protein C derivative lacking the gamma-carboxyglutamic acid domain, which is required for %binding% to %EPCR%, are not altered by the anti-%EPCR% %antibodies%. These data indicate that the protein C activation complex involves protein C, thrombin, thrombomodulin, and %EPCR%. These observations open new questions about the control of coagulation reactions on vascular endothelium.

%1996%

15/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10478349 BIOSIS NO.: 199699099494
The endothelial cell %protein% %C% %receptor%
Cell surface
expression and direct ligand %binding% by the soluble receptor.
AUTHOR: Fukudome Kenji; Kurosawa Shinichiro; Stearns-Kurosawa
Deborah J; He
Xuhua; Rezaie Alireza R; Esmen Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular
Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7**USA
JOURNAL: Journal of Biological Chemistry 271 (29):p17491-17498
%1996%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of the endothelial cell %protein%
%C%
%receptor% (%EPCR%) gene in mammalian cells imparts
the capacity
to %bind% activated protein C (APC) or protein C.
Immunohistochemical
analysis of CCD41, apparently the murine homologue of %EPCR%,
suggested centrosomal localization, raising questions about the location
of the %EPCR% gene product and its role in protein C
%binding%.
In this study, we express a soluble form of %EPCR%, demonstrate
%EPCR% expression on the cell surface, and direct
%binding%
between soluble %EPCR% and protein C/APC. Affinity purified
polyclonal and a monoclonal %antibody% against
%EPCR% %bound%
to the cell surface of %EPCR%-transfected cells but not to control
cells. A 49-kDa protein, a mass similar to soluble %EPCR%, was
immunoprecipitated from the cell surface of endothelium and cells
transfected with human %EPCR% but not from control cells. The
FLAG
%antibody% and APC %bound% to cells expressing an
%EPCR%
construct containing the FLAG epitope located in a putative extracellular
domain, whereas an %EPCR% construct truncated just before the
putative transmembrane domain produced only soluble %EPCR%
antigen.
Soluble %EPCR% inhibited APC %binding% to
%EPCR% expressing
cells in a concentration-dependent fashion, K-d(app) = 29 nM and
%bound% to immobilized protein C in a Ca-2+-dependent fashion.
Thus,
%EPCR% is a type I transmembrane protein that %binds%
directly to
APC.

%1996%

15/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10477211 BIOSIS NO.: 199699098356
The endothelial cell %protein% %C% %receptor%
Inhibition of
activated protein C anticoagulant function without modulation of reaction
with proteinase inhibitors.
AUTHOR: Regan Lisa M; Stearns-Kurosawa Deborah J; Kurosawa
Shinichiro;
Mollica Jeff; Fukudome Kenji; Esmen Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular
Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7**USA
JOURNAL: Journal of Biological Chemistry 271 (29):p17499-17503
%1996%
ISSN: 0021-9258

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A soluble form of the endothelial cell %protein%
%C%
%receptor% (%EPCR%) was analyzed for the ability to
modulate the
functional properties of protein C and activated protein C (APC). In a
plasma clotting system initiated with factor Xa, %EPCR% blocked
the
anticoagulant activity of APC in a dose-dependent fashion.
%EPCR% had
no influence on clotting in the absence of APC. Consistent with the
plasma results, %EPCR% slowed the proteolytic inactivation of
factor
Va by slowing both of the key proteolytic cleavages in the heavy chain of
factor Va. %EPCR% did not prevent protein C activation by the
soluble
thrombin-thrombomodulin complex, did not alter the inactivation of APC by
alpha-1-antitrypsin or protein C inhibitor, and did not influence the
kinetics of peptide paranitroanilide substrate cleavage significantly. We
conclude that %EPCR% %binds% to an exosite on APC
that
selectively modulates the enzyme specificity in a manner reminiscent of
the influence of thrombomodulin on thrombin.

%1996%

15/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10288691 BIOSIS NO.: 199698743609
The Gla-26 residue of protein C is required for the %binding% of
protein C to thrombomodulin and endothelial cell %protein%
%C%
%receptor%, but not protein S and factor Va.
AUTHOR: Nishioka Junji; Ido Masaru; Hayashi Tatsuya; Suzuki Koji(a)
AUTHOR ADDRESS: (a)Dep. Mol. Pathobiol., Mie Univ. Sch. Med.,
Tsu-city, Mie
514**Japan
JOURNAL: Thrombosis and Haemostasis 75 (2):p275-282 %1996%
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A functionally defective protein C (PC)-Mie, detected in the
plasma of a patient with hereditary thrombophilia, has Lys substituted
for gamma-carboxyglutamic acid (Gla)-26 residue. The activation rate of
PC-Mie by Protac or thrombin in the absence of Ca-2+ and that by thrombin
with native thrombomodulin (TM), recombinant soluble truncated TM or on
cultured endothelial cells in the presence of Ca-2+ were all apparently
lower than that of normal PC. The anticoagulant activity of
Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of
inactivation of factor Va by APC-Mie in the presence of phospholipids
were lower than those seen with normal APC. APC-Mie and normal APC
%bound% equally to protein S and to biotinyl-factor Va. However,
neither PC-Mie nor APC-Mie %bound% to phospholipids and to
cultured
human endothelial cells. It was similar to that observed with
Gla-domainless PC/APC, but different from that seen with normal PC/APC.
These results suggest that Gla-26-dependent conformation is required for
the %binding% of PC/APC to phospholipids, TM and the surface of
endothelial cell PC/APC receptor, but not to protein S and factor Va.

%1996%

15/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09765091 BIOSIS NO.: 199598220009
Molecular cloning and expression of murine and bovine endothelial cell
protein C/activated %protein% %C% %receptor%

(%%EPCR%%):

The structural and functional conservation in human, bovine and murine
%%EPCR%%.

AUTHOR: Fukudome Kenji; Esmon Charles T(a)

AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res.
Found., 825

NE 13, Oklahoma City, OK 73104**USA

JOURNAL: Journal of Biological Chemistry 270 (10):p5571-5577

%%1995%%

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Recently, we identified and cloned a human endothelial cell
protein C/activated %%protein%% %%C%% %%receptor%%
(%%EPCR%%).

%%EPCR%% was predicted to be a type I transmembrane glycoprotein
and a

novel member of the CD1/major histocompatibility complex superfamily
with

28% identity with CD1d. Even greater homology (62% identity) was
detected

with the murine protein, CCD41, which was previously characterized as a
centrosome-associated, cell cycle-dependent protein. This raised the
possibility that CCD41 was the murine homologue of %%EPCR%%. To

address
this possibility, to better understand structure-function relationships,
and to facilitate physiological experiments on %%EPCR%% function,

we

cloned and sequenced murine and bovine %%EPCR%% from
endothelial cell

cDNA libraries. The nucleotide sequence of murine %%EPCR%% and
CCD41

exhibited five differences corresponding to one base change, three
single-base insertions, and one base deletion in the protein coding
region. As a result, the predicted structures of %%EPCR%% and
CCD41

differed in their amino and carboxyl termini but were identical in the
central portion of the coding sequence. Based on comparison of the
murine, bovine, and human %%EPCR%% sequences and the regions
where

discrepancies between murine %%EPCR%% and CCD41 were
detected, we

believe that CCD41 is probably identical to murine %%EPCR%% and
that

the reported sequence differences are likely the result of compression on
the sequencing gel. Compared with human %%EPCR%%, the murine
and bovine

sequences were 69 and 73% identical, respectively, and 57% of the
residues were identical between all three species. Both bovine and murine
%%EPCR%% could %%bind%% human activated protein C when
the cDNA

clones were transfected into 293T cells. Like human %%EPCR%%, of
the

cell lines tested, the murine %%EPCR%% message was restricted to
endothelium. Cloning of the murine and bovine homologue of

%%EPCR%%

will facilitate in vivo and in vitro studies of the role of %%EPCR%% in
the protein C pathway.

%%1995%%

15/3,AB/10 (Item 10 from file: 5)

DIALOG(R)File 5:BIOSIS Previews(R)

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09545786 BIOSIS NO.: 199598000704

Identification, Cloning, and Regulation of a Novel Endothelial Cell Protein
C/Activated %%Protein%% %%C%% %%Receptor%%.

AUTHOR: Fukudome Kenji; Esmon Charles T(a)

AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res.
Foundation,

825 NE 13, Oklahoma City, OK 73104**USA

JOURNAL: Journal of Biological Chemistry 269 (42):p26486-26491

%%1994%%

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Human protein C and activated protein C are shown to
%%bind%%

to endothelium specifically, selectively, and saturably (K-d = 30 nM,
7000 sites per cell) in a Ca-2+-dependent fashion. Expression cloning
revealed a 1.3-kilobase pair cDNA that coded for a novel type I
transmembrane glycoprotein capable of %%binding%% protein C. This
protein appears to be a member of the CD1/major histocompatibility
complex superfamily. Like thrombomodulin, the receptor involved in
protein C activation, the endothelial cell %%protein%% %%C%%
%%receptor%% function and message are both down-regulated by

exposure

of endothelium to tumor necrosis factor. Identification of endothelial
cell %%protein%% %%C%% %%receptor%% as a member of
the CD1/major
histocompatibility complex superfamily provides insights into the role of
protein C in regulating the inflammatory response.

%%1994%%

15/3,AB/11 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

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06422492 EMBASE No: 1996085709

The Glasup 2sup 6 residue of protein C is required for the

%%binding%%

of protein C to thrombomodulin and endothelial cell %%protein%%
%%C%%

%%receptor%%, but not to protein S and factor Va

Nishioka J.; Ido M.; Hayashi T.; Suzuki K.

Department of Molecular Pathobiology, Mie University School of
Medicine, Tsu-city, Mie 514 Japan

Thrombosis and Haemostasis (THROMB. HAEMOST.) (Gennany) 1996,
75/2

(275-282)

CODEN: THHAD ISSN: 0340-6245

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

A functionally defective protein C (PC)-Mie, detected in the plasma of a
patient with hereditary thrombophilia, has Lys substituted for
gamma-carboxyglutamic acid (Gla)sup 2sup 6 residue. The activation rate of
PC-Mie by Protac or thrombin in the absence of Casup 2sup + and that by
thrombin with native thrombomodulin (TM), recombinant soluble truncated
TM

or on cultured endothelial cells in the presence of Casup 2sup + were all
apparently lower than that of normal PC. The anticoagulant activity of
Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of
inactivation of factor Va by APC-Mie in the presence of phospholipids were
lower than those seen with normal APC, APC-Mie and normal APC
%%bound%%

equally to protein S and to biotinyl-factor Va. However, neither PC-Mie nor
APC-Mie %%bound%% to phospholipids and to cultured human
endothelial

cells. It was similar to that observed with Gla-domainless PC/APC, but
different from that seen with normal PC/APC. These results suggest that
Glasup 2sup 6-dependent conformation is required for the
%%binding%% of
PC/APC to phospholipids, TM and the surface of endothelial cell PC/APC
receptor, but not to protein S and factor Va.

15/3,AB/12 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08488479 96124295

Cellular regulation of the protein C pathway.

Esmon CT; Fukudome K

Oklahoma Medical Research Foundation, Department of Pathology,
University

of Oklahoma Health Sciences Center, Oklahoma City 73104, USA.

Seminars in cell biology (UNITED STATES) Oct %%1995%%, 6 (5)

p259-68

, ISSN 1043-4682 Journal Code: A60

Contract/Grant No.: R37 HL30340, HL, NHLBI; R01 HL 29807, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

The protein C anticoagulant pathway regulates thrombin formation. The pathway is triggered when thrombin binds to the endothelial cell

proteoglycan, thrombomodulin. Unlike thrombin, this complex is a potent activator of the protein C zymogen, but it cannot clot blood. Activated protein C binds to protein S on cell surfaces where it proteolytically inactivates coagulation factors Va and VIIIa. Activated protein C also binds to a newly identified endothelial

protein receptor. Congenital deficiencies in this pathway are associated with thrombotic disease, and inflammation can cause acquired deficiencies. Activated protein C appears to inhibit inflammation. Thus, this pathway modulates both coagulation and inflammation.

15/3,AB/13 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08115399 95159086

High affinity binding sites for activated protein C and protein C

on cultured human umbilical vein endothelial cells. Independent of protein S and distinct from known ligands.

Bangalore N; Drohan WN; Ortlimer CL

Plasma Derivatives Laboratory, American Red Cross Holland Laboratory, Rockville, Maryland 20855.

Thrombosis and haemostasis (GERMANY) Sep 1994, 72 (3) p465-74,

ISSN 0340-6245 Journal Code: VQ7

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Activated protein C (APC) is an antithrombotic serine proteinase having anticoagulant, profibrinolytic and anti-inflammatory activities. Despite its potential clinical utility, relatively little is known about its clearance mechanisms. In the present study we have characterized the interaction of APC and its active site blocked forms with human umbilical vein endothelial cells (HUVEC). At 4 degrees C 125I-APC

bound to HUVEC in a specific, time dependent, saturable and reversible manner. Scatchard analysis of the binding isotherm demonstrated a Kd

value of 6.8 nM and total number of binding sites per cell of 359,000.

Similar

binding isotherms were obtained using radiolabeled protein C (PC)

zymogen as well as D-phe-pro-arg-chloromethylketone (PPACK) inhibited APC

indicating that a functional active site was not required. Competition studies showed that the binding of APC, PPACK-APC and PC were

mutually exclusive suggesting that they bound to the same site(s).

Proteolytic removal of the N-terminal gamma-carboxyglutamic acid (gla) domain of PC abolished its ability to compete indicating that the gla-domain was essential for cell binding. Surprisingly, APC

binding to these cells appeared to be independent of protein S, a

cofactor of APC generally thought to be required for its high affinity

binding to cell surfaces. The identity of the cell

binding

site(s), for the most part, appeared to be distinct from other known APC

ligands which are associated with cell membranes or extracellular matrix including phospholipid, thrombomodulin, factor V, plasminogen activator

inhibitor type 1 (PAI-1) and heparin. Pretreatment of HUVEC with antifactor VIII antibody caused partial inhibition of 125I-APC

binding

indicating that factor VIII or a homolog accounted for approximately 30% of APC binding. Studies of the properties of surface

bound

125I-APC or 125I-PC and their fate at 4 degrees C compared to 37 degrees C

were consistent with association of approximately 25% of the initially

radioligand with an endocytic receptor. However, most of the

radioligand appeared not to be bound to an endocytic receptor and

dissociated rapidly at 37 degrees C in an intact and functional state.

These data indicate the presence of specific, high affinity

binding

sites for APC and PC on the surface of HUVEC. While a minor proportion

of

binding sites may be involved in endocytosis, the identity

and

function of the major proportion is presently unknown. It is speculated

that this putative receptor may be a further mechanisms of localizing the

PC antithrombotic system to the vascular endothelium.

15/3,AB/14 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotechnology Abs

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0194874 DBA Accession No.: 96-05645 PATENT

Isolated endothelial cell protein-C/activated

protein-C receptor - gene cloning and expression for use as an

antiinflammatory or anticoagulant; inhibitory nucleic acid for use in cancer therapy; antitumor receptor-antagonist isolation

AUTHOR: Fukudome K; Esmen C T

CORPORATE SOURCE: Oklahoma City, OK, USA.

PATENT ASSIGNEE: Oklahoma-Med.Res.Found. 1996

PATENT NUMBER: WO 9605303 PATENT DATE: 960222 WPI

ACCESSION NO.:

96-139699 (9614)

PRIORITY APPLIC. NO.: US 289699 APPLIC. DATE: 940812

NATIONAL APPLIC. NO.: WO 95US9636 APPLIC. DATE: 950809

LANGUAGE: English

ABSTRACT: A new isolated human endothelial cell protein-C-activated-

protein-C receptor has a specified

DNA sequence or

derivative, and may be expressed on the surface of a non-human cell or

non-endothelial cell, or may be in soluble form (lacking at least part

of the transmembrane region). The DNA may be inserted in a vector for

expression in a host cell. An inflammatory response may be enhanced by

blocking binding of protein-C (EC-3.4.21.69) or

activated

protein-C to the receptor using an antibody or fragment,

inhibitory nucleic acid or other types of compound. An inflammatory

response may be inhibited using the receptor or an agonist. These

antiinflammatory compounds may be useful in therapy of e.g.

Gram-negative bacterium sepsis, apoplexy, thrombosis, septic shock,

acute respiratory distress syndrome or pulmonary embolism. Localization

of the receptor to surfaces in contact with blood renders the surfaces

anticoagulant by concentration of activated protein-C, so may be used

in coating of vascular grafts. Receptor-antagonists may be useful as

e.g. antitumor agents. (58pp)

? ds

Set Items Description

S1 27187 PROTEIN(W)C

S2 96 EPCR

S3 134 S1(W)RECEPTOR

S4 147 S2 OR S3

S5 1478948 ANTIBOD?

S6 7599752 TREAT? OR DIAGNOS?

S7 26 S4 AND S5

S8 3969 S1 AND S5

S9 1759385 BIND? OR BOUND

S10 2429 S1(N5)S9

S11 423 S10 AND S6

S12 76 S4 AND S9

S13 78 S7 OR S12

S14 39 RD (unique items)

S15 14 S14 AND PY<1998

? s s1(2n)s9

27187 S1
1759385 S9
S16 1775 S1(2N)S9
? s s16 and s6

1775 S16
7599752 S6
S17 329 S16 AND S6
? rd

...examined 50 records (50)
...examined 50 records (100)
...examined 50 records (150)
...examined 50 records (200)
...examined 50 records (250)
...examined 50 records (300)
...completed examining records
S18 167 RD (unique items)
? s s18 and py<1998

Processing
167 S18
28044798 PY<1998
S19 92 S18 AND PY<1998
? t s19/3,ab/1-92

19/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11295524 BIOSIS NO.: 199800076856
CCAAT/enhancer-binding protein delta activates insulin-like growth factor-I gene transcription in osteoblasts: Identification of a novel cyclic AMP signalling pathway in bone.
AUTHOR: Umayahara Yutaka; Ji Changhua; Centrella Michael; Rotwein Peter(a);
McCarthy Thomas L
AUTHOR ADDRESS: (a)Oregon Health Sci. Univ., Dep. Med., Molecular Med.
Div., 3181 S.W. Sam Jackson Park Rd., Mail C**USA
JOURNAL: Journal of Biological Chemistry 272 (50):p31793-31800 Dec. 12,
1997
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Insulin-like growth factor-I (IGF-I) plays a key role in skeletal growth by stimulating bone cell replication and differentiation. We previously showed that prostaglandin E2 (PGE2) and other cAMP-activating agents enhanced, IGF-I gene transcription in cultured primary rat osteoblasts through promoter 1, the major IGF-I promoter, and identified a short segment of the promoter, termed HS3D, that was essential for hormonal regulation of IGF-I gene expression. We now demonstrate that CCAAT/enhancer-binding protein (C/EBP) delta is a major component of a PGE2-stimulated DNA-protein complex involving HS3D and find that C/EBPdelta transactivates IGF-I promoter 1 through this site. Competition gel shift studies first indicated that a core C/EBP half-site (GCAAT) was required for binding of a labeled HS3D oligomer to osteoblast nuclear proteins. Southwestern blotting and UV-cross-linking studies showed that the HS3D probe recognized a approx 35-kDa nuclear protein, and antibody supershift assays indicated that C/EBPdelta comprised most of the PGE2-activated gel-shifted complex. C/EBPdelta was detected by Western immunoblotting in osteoblast nuclear extracts after treatment of cells with PGE2. An HS3D oligonucleotide competed effectively with a high affinity C/EBP site from the rat albumin gene for binding to osteoblast nuclear proteins. Cotransfection of osteoblast cell cultures with a C/EBPdelta expression plasmid enhanced basal and PGE2-activated IGF-I promoter 1-luciferase activity but did not stimulate a reporter gene lacking an HS3D site. By contrast, an expression plasmid for the related protein, C/EBPbeta, did not alter basal IGF-I gene

activity but did increase the response to PGE2. In osteoblasts and in COS-7 cells, C/EBPdelta, but not C/EBPbeta, transactivated a reporter gene containing four tandem copies of HS3D fused to a minimal promoter; neither transcription factor stimulated a gene with four copies of an HS3D mutant that was unable to bind osteoblast nuclear proteins. These results identify C/EBPdelta as a hormonally activated inducer of IGF-I gene transcription in osteoblasts and show that the HS3D element within IGF-I promoter 1 is a high affinity binding site for this protein.

1997

19/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11264512 BIOSIS NO.: 199800045844
Transcription factor C/EBPdelta in fetal lung: Developmental regulation and effects of cyclic adenosine 3',5'-monophosphate and glucocorticoids.
AUTHOR: Breed David R; Margraf Linda R; Alcorn Joseph L; Mendelson Carole R
(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Univ. Texas Southwestern Med. Center,
5323 Harry Hines Blvd., Dallas, TX 75235-90**USA
JOURNAL: Endocrinology 138 (12):p5527-5534 Dec., 1997
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pulmonary surfactant is a developmentally and hormonally regulated lipoprotein synthesized exclusively in alveolar type II cells. Surfactant protein-A (SP-A) gene transcription in human fetal lung in culture is stimulated by glucocorticoids and cAMP; cAMP also enhances the rate of type II cell differentiation. The CCAAT/enhancer-binding protein (C/EBP) family of transcription factors serves an important role in the regulation of genes involved in energy metabolism, lipid biosynthesis, and cellular differentiation. The gene encoding C/EBPdelta, which is induced by glucocorticoids during the early phases of adipocyte differentiation, is expressed at relatively high levels in lung compared with other tissues. In the present study we have analyzed developmental changes in C/EBPdelta messenger RNA levels in fetal rabbit lung as well as changes in the levels of immunoreactive C/EBPdelta in human fetal lung during differentiation in organ culture and after treatment with cAMP and glucocorticoids. We observed that C/EBPdelta messenger RNA is detectable in fetal rabbit lung on day 19 of gestation and is increased 3.7-fold to maximum levels on day 28 of gestation, the time when SP-A gene transcription increases to maximum levels. Immunohistochemical analysis of C/EBPdelta in midgestation human fetal lung before culture revealed trace nuclear staining in epithelial and occasional stromal cells. After 12 h of organ culture in serum-free medium, nuclear staining of C/EBPdelta was markedly increased in epithelial cells lining the prealveolar ducts of the human fetal lung tissue. By immunoblot analysis, it was found that C/EBPdelta levels were induced rapidly during organ culture in control medium and were increased further by treatment with dexamethasone and (Bt)2cAMP. C/EBPdelta levels were maximally induced during the first 24 h of culture and declined thereafter; after 72 h of incubation in control or cAMP-containing medium, C/EBPdelta was reduced markedly. By contrast, in fetal lung tissues incubated in medium containing dexamethasone or dexamethasone plus (Bt)2cAMP, the decline in C/EBPdelta was more modest, so that levels remained elevated throughout the 96-h culture period. Our findings that C/EBPdelta is localized primarily to alveolar epithelial cells, rapidly induced during differentiation of human fetal lung in culture, and increased by cAMP and glucocorticoids suggest a possible role in the regulation of type II cell differentiation and in the synthesis of surfactant phospholipids and proteins.

1997

19/3,AB/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11261929 BIOSIS NO.: 199800043261

Physical activity and biochemical markers of bone turnover in elderly patients.

AUTHOR: Ricciotti Roberto(a); Gemini Rossano; Foschi Ferdinando; Dubbini

Stefania; Fattoretti Patrizia; Bertoni-Freddari Carlo

AUTHOR ADDRESS: (a)Radiochemistry Lab., INRCA, Via della Montagonal 164,
60131 Ancona**Italy

JOURNAL: Archives of Gerontology and Geriatrics 26 (1):p49-53 Dec.,
%%1997%%

ISSN: 0167-4943

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: To assess the role of physical therapy in improving the remodelling processes of bone turnover, biochemical markers of bone formation and resorption (osteocalcin, parathormone, bone-specific alkaline phosphatase, somatotrophic hormone, C-terminal propeptide type I procollagen, somatomedin, insulin-like growth factor %bound% %protein%, %C%-terminal telopeptide type I collagen) have been

investigated in elderly patients before and after a cycle of physical therapy. Patients of both sexes, immobilized on hospital admission day because of fractures or neurologic diseases, underwent physiotherapy for one month. Following physical %treatment% we found significant increases of osteocalcin, bone-specific alkaline phosphatase and somatomedin in the female group, while no significant difference was detected in males. Our data support that the mechanical stimulus significantly improves the recovery of osteoblastic activity in women, while in men the increases in bone remodelling markers are not significant. Differences in life-style between male and female patients are proposed as determinants in the bone remodelling response to physical therapy.

%%1997%%

19/3,AB/4 (Item 4 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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11248145 BIOSIS NO.: 199800029477

Clinical characteristics of familial hypertrophic cardiomyopathy caused by the Phe110Ile mutation in the cardiac troponin T gene: Analysis of 6 families.

AUTHOR: Shono Hirohisa(a)

AUTHOR ADDRESS: (a)First Dep. Internal Med., Fac. Med., Kagoshima Univ.,

Kagoshima 890**Japan

JOURNAL: Medical Journal of Kagoshima University 49 (2):p117-128 Aug.,

%%1997%%

ISSN: 0368-5063

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Japanese; Non-English

SUMMARY LANGUAGE: Japanese; English

ABSTRACT: To clarify the genetic and clinical features of familial hypertrophic cardiomyopathy (FHC) caused by a Phe110Ile mutation in the cardiac troponin T (TnT) gene, 6 families with Phe110Ile mutation were studied. Forty-six probands (24 males, 22 females, age 57.4+-17.1 years old) with FHC were screened for mutations in beta cardiac myosin heavy chain, alpha-tropomyosin, TnT and cardiac myosin %binding% %protein%-%%C% genes. Phe110Ile mutation in TnT gene was found in

probands. Family survey was done in the 6 families. Genetic analyses were done with mutation analysis and haplotype analysis. Clinical analyses were done with electrocardiograms and echocardiograms. Left ventricular hypertrophy was evaluated with echocardiograms. According to Maron's criteria, distribution of the hypertrophy was classified into type I, II, III and IV. Apical hypertrophy was classified as type IV (A). Genotyping of angiotensin-I converting enzyme (ACE) gene was done in 14 members in

4

families. Phenotype of the 6 probands was type II in 2 probands, type III in 2 (1 with left ventricular outflow obstruction) and type IV(A) in 2. Twenty members in 6 families were analyzed genetically and clinically. Sixteen (5 males, 11 females, age 47.9+-16.6 years old) were affected with Phe110Ile mutation by mutation analysis. Two of the 6 families will be the same origin by haplotype analysis, while 4 will be different each other. Phenotype of the affected members was type II in 4 members, type III in 6 (1 with left ventricular outflow obstruction), type IV (A) in 3 and nonpenetrance in 3. Mean maximal wall thickness of the left ventricle in affected subjects was 17.3+-4.8mm, and penetrance of the mutation was 81%. More than 2 affected members were analyzed in 4 families. Phenotype of 2 affected members was same in 1 family, but phenotype of affected members were different in other 3 families. In one family, phenotype was type IV(A) in 2 members, nonpenetrance was in 1. In another family, phenotype was type IV (A) in 1 member, type II in 1, type III in 2, nonpenetrance in 1. In the other family, phenotype was type II in 2 members, type III in 1, nonpenetrance in 1. No correlation was found with ACE genotype and wall thickness nor type of the hypertrophy. It was suggested that distribution of the hypertrophy was various (type II, III, IV(A)) in FHC with Phe110Ile mutation in TnT gene, and that it was not always identical within a family.

%%1997%%

19/3,AB/5 (Item 5 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

11177515 BIOSIS NO.: 199799798660

Hepatic expression of CCAAT/enhancer binding protein alpha: Hormonal and metabolic regulation in rats.

AUTHOR: Crosson S M; Davies G F; Roesler W J(a)

AUTHOR ADDRESS: (a)Dep. Biochem., Univ. Sask., 107 Wiggins Rd., Saskatoon,

SK S7N 5E5**Canada

JOURNAL: Diabetologia 40 (10):p1117-1124 %%1997%%

ISSN: 0012-186X

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: There is a significant body of evidence which suggests that the alpha-isoform of the CCAAT/enhancer %binding%

%protein% (%C%)

/EBP-alpha) plays a central regulatory role in energy metabolism in the liver. However, there is little information available regarding regulation of its expression in this tissue. In this study, we examined the effect of hormones and diabetes on its expression in rat H4IIE hepatoma cells and in rat liver. %Treatment% of H4IIE cells with dexamethasone led to a threefold increase in C/EBP-alpha mRNA within 4 h.

Insulin %treatment% produced a bi-phasic response, initially reducing mRNA levels up to the 4 h time point, but after 8 h a twofold increase in C/EBP-alpha mRNA was observed. %Treatment% with 8-chlorophenylthio-cAMP produced a twofold induction of C/EBP-alpha mRNA

after 8 h. Western analysis indicated that the changes in mRNA in response to hormonal %treatment% generally resulted in corresponding alterations in C/EBP-alpha protein levels. Finally, we observed an inhibition of C/EBP-alpha gene expression in streptozotocin-diabetic rat liver, reflected by a decrease in both mRNA and protein levels that were partially reversed by insulin %treatment%. These results indicate that the expression of C/EBP-alpha in liver is under complex control by both hormonal and metabolic signals, which is consistent with its role as a trans-regulator of genes which play a role in energy metabolism.

%%1997%%

19/3,AB/6 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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11023149 BIOSIS NO.: 199799644294

Thrombomodulin gene mutations associated with myocardial infarction.

AUTHOR: Ireland Helen(a); Kunz Gabriella; Kyriakoulis Konstantinos; Stubbs
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 Dunstons Rd., London W6 8RP**UK
 JOURNAL: Circulation 96 (1):p15-18 %%%1997%%
 ISSN: 0009-7322
 RECORD TYPE: Abstract
 LANGUAGE: English

ABSTRACT: Background: Thrombomodulin is an important receptor for thrombin on the endothelial cell surface of most blood vessels, including those of the heart. Thrombin-%%bound%% thrombomodulin activates %%%protein%% %%%C%%, which inhibits thrombin generation by degrading factors Va and VIIIa. The aim of this study was to analyze the 5' region of the thrombomodulin gene to determine whether mutations contribute a risk for myocardial infarction. Methods and Results: We screened the promoter region of the thrombomodulin gene by single-stranded conformation polymorphism analysis in 104 patients with %%%diagnosed%% myocardial infarction. Five mutations (three distinct) were identified (GG-9/-10AT, G-33A, and C-133A). The dinucleotide mutation GG-9/-10AT was identified in 3 individuals (2 heterozygous, 1 homozygous). Only one of the three different mutations was identified in 104 patient control subjects matched for age, sex, and race (G-33A in a single individual). All mutations identified were in close proximity to consensus sequences for transcription control elements within the thrombomodulin gene. In contrast, no difference was observed between patients and control subjects for the allelic frequency of a previously identified neutral polymorphism GCC/GTC coding for Ala/Val-455, with 3 individuals homozygous for GTC (Val) in both groups. Conclusions The findings suggest that mutations in the promoter region of the thrombomodulin gene may constitute a risk for arterial thrombosis.

%%1997%%

19/3,AB/7 (Item 7 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
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10989822 BIOSIS NO.: 199799610967
 CCAAT/enhancer binding protein epsilon is preferentially up-regulated during granulocytic differentiation and its functional versatility is determined by alternative use of promoters and differential splicing.
 AUTHOR: Yamanaka Ryuya; Kim Gun-Do; Radomska Hanna S; Lekstrom-Himes Julie; Smith Laura T; Antonson Per; Tenen Daniel G; Xanthopoulos Kleanthis G(a)
 AUTHOR ADDRESS: (a)Clinical Gene Therapy Branch, Natl. Hum. Genome Res. Inst., Build. 10, Room 10C103, Natl. Inst. **USA
 JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 94 (12):p6462-6467 %%%1997%%
 ISSN: 0027-8424
 RECORD TYPE: Abstract
 LANGUAGE: English

ABSTRACT: CCAAT/enhancer %%%binding%% %%%protein%% (%%%C%%/EBP) epsilon is a recently cloned member of the C/EBP family of transcription factors and is expressed exclusively in cells of hematopoietic origin. The human C/EBP-epsilon gene is transcribed by two alternative promoters, P-alpha and P-beta. A combination of differential splicing and alternative use of promoters generates four mRNA isoforms, of 2.6 kb and 1.3-1.5 kb in size. These transcripts can encode three proteins of calculated molecular mass 32.2 kDa, 27.8 kDa, and 14.3 kDa. Accordingly, Western blots with antibodies specific for the DNA-binding domain, that is common to all forms, identify multiple proteins. C/EBP-epsilon mRNA was greatly induced during in vitro granulocytic differentiation of human primary CD34+ cells. Retinoic acid %%%treatment%% of HL60 promyelocytic leukemia cells

for 24 hr induced C/EBP-epsilon mRNA levels by 4-fold, while prolonged %%%treatment%% gradually reduced mRNA expression to pretreatment levels.

Transient transfection experiments with expression vectors for two of the isoforms demonstrated that the 32.2-kDa protein is an activator of transcription of granulocyte colony-stimulating factor receptor promoter, while the 14.3-kDa protein is not. Thus, C/EBP-epsilon is regulated in a complex fashion and may play a role in the regulation of genes involved in myeloid differentiation.

%%1997%%

19/3,AB/8 (Item 8 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
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10970292 BIOSIS NO.: 199799591437
 Cardiomyopathies.
 AUTHOR: Schwartz Ketty
 AUTHOR ADDRESS: IFR n. 14, INSERM UR 153, Inst. Myol., Groupe Hosp. Pitie-Salpetriere, 47 boulevard de l'Hopital, 75**France
 JOURNAL: Pathologie Biologie 45 (3):p213-217 %%%1997%%
 ISSN: 0369-8114
 RECORD TYPE: Abstract
 LANGUAGE: English
 SUMMARY LANGUAGE: English; French

ABSTRACT: Cardiomyopathies, and more specifically hypertrophic cardiomyopathy, have opened the route to what is now called genetic cardiology. Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left and/or right ventricular hypertrophy, and disorganization of tissular architecture. Approximately 60% of HCM are transmitted as an autosomal dominant trait. The clinical aspects of HCM vary markedly, and several morphological variants were described, depending on the localization of hypertrophy. This pathology is often complicated by cardiac failure, but the major risk is sudden death, and the predictive factors are presently very unrefined. Several pathogenic hypotheses were forwarded in the past, and one surprising result of genetic analyses is that none of these hypotheses was confirmed. Four disease genes were identified, and they encode sarcomeric proteins, cardiac myosin heavy chain, troponin T, tropomyosin and cardiac myosin %%%binding%% %%%protein%% %%%C%%. To this high intergenic

heterogeneity is associated a high intragenic heterogeneity. A major fall out of these genetic findings is the recent discovery of adult healthy carriers, around 30% in our experience. Genotype/phenotype relationships are being performed, and this is the first approach to a prognostic evaluation based on genetic localization. The work on hypertrophic cardiomyopathy is currently being used as a model to analyse dilated cardiomyopathies, characterized by dilatation and impaired contraction of the left or both ventricles. The mode of inheritance of these forms of cardiomyopathies is complex. Five families with an autosomal inheritance were analyzed since two years, the loci were found, but the disease genes are not identified yet. Identification of patients at high risk and early %%%treatment%% or prevention are the current goals.

%%1997%%

19/3,AB/9 (Item 9 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
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10834266 BIOSIS NO.: 199799455411
 Functional antagonism between CCAAT/enhancer binding protein-alpha and peroxisome proliferator-activated receptor-gamma on the leptin promoter.
 AUTHOR: Hollenberg Anthony N; Susulic Vedula S; Madura John P; Zhang Bei; Moller David E; Tontonoz Peter; Sarraf Pasha; Spiegelman Bruce M; Lowell Bradford B(a)
 AUTHOR ADDRESS: (a)Division Endocrinol., Beth Israel Hosp., Harvard Med. Sch., Boston, MA 02215**USA
 JOURNAL: Journal of Biological Chemistry 272 (8):p5283-5290
 %%%1997%%

ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ob gene product, leptin, is a major hormonal regulator of appetite and fat cell mass. Recent work has suggested that the antidiabetic agents, the thiazolidinediones (TZ), which are also high affinity ligands of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), inhibit leptin expression in rodents. To examine the effects of this class of drug on the leptin gene in adipocytes we performed Northern analysis on primary rat adipocytes cultured in the presence or absence of TZ. TZ reduced leptin mRNA levels by 75%. To determine whether this effect was mediated at the transcriptional level, we isolated 6510 base pairs of 5'-flanking sequence of the leptin promoter and studied reporter constructs in primary rat adipocytes and CV-1 cells. Sequence analysis demonstrated the presence of a consensus direct repeat with a 1-base-pair gap site between -3951 and -3939 as well as a consensus CCAAT/enhancer binding site (C/EBP) site between -55 and -47. Our functional analysis in transfected primary rat adipocytes demonstrates that, despite the presence of a canonical direct repeat with a 1-base-pair gap site, TZ alone decreases reporter gene expression of leptin promoter constructs ranging from -6510 to +9 to -65 to +9. In CV-1 cells, which contain endogenous PPAR-gamma, TZ alone had little effect on these constructs. However, TZ

did inhibit C/EBP α -mediated transactivation of the leptin promoter. This down-regulation of leptin reporter constructs mapped to a -65 to +9 promoter fragment which binds C/EBP α in gel-mobility shift assays but does not bind PPAR-gamma-2 alone or as a heterodimer with 9-cis-retinoic acid receptor. Conversely, the promoter (-5400 to +24 base pairs) of the aP2 gene, another adipocyte-specific gene, was induced 7.3-fold by TZ. Co-transfection with C/EBP α minimally stimulated the aP2 promoter from basal levels but notably blocked activation by TZ. These data indicate that PPAR-gamma and C/EBP α can functionally antagonize each other on at least two separate promoters and that this mechanism may explain the down-regulation of leptin expression by thiazolidinediones.

1997

19/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10802420 BIOSIS NO.: 199799423565
The glucocorticoid-responsive gene cascade: Activation of the rat arginase gene through induction of C/EBP-beta.
AUTHOR: Gotoh Tomomi; Chowdhury Shoaib; Takiguchi Masaki(a); Mori Masataka
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JOURNAL: Journal of Biological Chemistry 272 (6):p3694-3698
1997
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The gene for liver-type arginase, an ornithine cycle enzyme, is induced by glucocorticoids in a delayed secondary manner. An enhancer element located around intron 7 of the rat arginase gene shows delayed glucocorticoid responsiveness, and it harbors two sites binding with members of the CCAAT/enhancer binding site (C/EBP) family. Here, we investigate the role of these C/EBP binding sites in glucocorticoid response of the arginase gene. When inserted in front of the herpes simplex virus thymidine kinase promoter, these C/EBP sites exhibited glucocorticoid responsiveness in reporter transfection assay using rat hepatoma H4IIE cells. In footprint analysis using nuclear extracts of H4IIE cells, profiles of the protected areas of the two C/EBP sites changed when cells were treated with dexamethasone. In gel shift analysis, the complex formation for the two C/EBP sites was augmented in response to dexamethasone. Antibody supershift/inhibition analysis demonstrated that a major portion of the binding proteins

induced by dexamethasone is C/EBP-beta. Induction of arginase mRNA by dexamethasone was preceded by augmentation of the C/EBP site-binding activities, which followed increase in C/EBP-beta mRNA. These results were consistent with the notion that the glucocorticoid response of the arginase gene is mediated by C/EBP-beta.

1997

19/3,AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10613362 BIOSIS NO.: 199699234507
Regulation of CCATT/enhancer-binding protein family members by stimulation of glutamate receptors in cultured rat cortical astrocytes.
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JOURNAL: Journal of Biological Chemistry 271 (38):p23520-23527
1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Regulation of mRNA levels, DNA binding activities, and phosphorylation of CCAAT/enhancer binding site (C/EBP) family members by stimulation of glutamate receptors were studied in cultured rat cortical astrocytes. Indirect immunofluorescence and immunoblot analyses with specific antibodies to C/EBP family members revealed that both C/EBP-beta and C/EBP-delta but not C/EBP-alpha are expressed in the nuclei of astrocytes. After exposure to glutamate, C/EBP-beta mRNA levels increased within 10 min, reached the maximal level at about 1 h, and returned to the basal level within 6 h. In contrast, C/EBP-delta mRNA levels decreased by 6 h and were recovered within 12 h. These changes in mRNA levels were accompanied by an increase and a decrease in proteins for C/EBP-beta and C/EBP-delta, respectively. Elevation of C/EBP-beta mRNA levels by glutamate treatment required an increase in intracellular Ca²⁺ concentration and depended on activations of protein kinase C and calmodulin-dependent protein kinases. Gel mobility shift analysis using nuclear extracts from the glutamate-treated cells showed increases in C/EBP site binding activities after the exposure to glutamate. Moreover, glutamate stimulated phosphorylation of C/EBP-beta in 32P-labeled astrocytes in a Ca²⁺-dependent manner. These results suggest that glutamate regulates functions of C/EBP family members in brain astrocytes through changes in mRNA levels of C/EBP-beta and C/EBP-delta as well as through phosphorylation of C/EBP-beta.

1996

19/3,AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10578217 BIOSIS NO.: 199699199362
CAMP activation of phosphoenolpyruvate carboxykinase transcription in renal LLC-PK-1-F+ cells.
AUTHOR: Liu Xiangdong; Curthoys Norman P(a)
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Fort Collins, CO 80523-1870**USA
JOURNAL: American Journal of Physiology 271 (2 PART 2):pF347-F355
1996
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Phosphoenolpyruvate carboxykinase (PCK) is a key regulatory enzyme in renal ammoniogenesis and gluconeogenesis. LLC-PK-1-F+ cells are porcine renal proximal tubule-like cells that express significant levels of the cytosolic PCK. Treatment of subconfluent LLC-PK-1-F+ cells with 0.1 mM 8-(4-chlorophenylthio)adenosine 3',5'-cyclic monophosphate (CPT-cAMP) for 8 h causes a 21-fold increase in PCK mRNA. This response is very rapid and is not inhibited by 0.5 mM cycloheximide, indicating that ongoing protein synthesis is not required. Similarly, cells transfected with PCK-490CAT exhibit an 8- to 10-fold increase in chloramphenicol acetyltransferase (CAT) activity when treated with cAMP for 24 h. The addition of okadaic acid, a protein phosphatase inhibitor, both stimulated the CAT activity and potentiated the cAMP effect by twofold, suggesting that phosphorylation may contribute to the transcriptional activation. Assays using a series of PCK-CAT constructs containing specific deletions or block mutations established that the CRE-1 and the P3(II) elements are required for the cAMP response. Cotransfection experiments using dominant negative expression vectors indicated that a CCAAT enhancer binding protein (C/EBP) transcription factor, and not CREB, mediates cAMP activation of transcription in LLC-PK-1-F+ cells.

1996

19/3,AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10526383 BIOSIS NO.: 199699147528
Alteration of myosin cross bridges by phosphorylation of myosin-binding protein in cardiac muscle.
AUTHOR: Weisberg Andrea; Winegrad Saul(a)
AUTHOR ADDRESS: (a)Dep. Physiol., Sch. Med., Univ. Pennsylvania, Philadelphia, PA 19104-6085**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (17):p8999-9003 1996
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In addition to the contractile proteins actin and myosin, contractile filaments of striated muscle contain other proteins that are important for regulating the structure and the interaction of the two force-generating proteins. In the thin filaments, troponin and tropomyosin form a Ca-sensitive trigger that activates normal contraction when intracellular Ca is elevated. In the thick filament, there are several myosin-binding proteins whose functions are unclear. Among these is the myosin-binding protein C (MBP-C). The cardiac isoform contains four phosphorylation sites under the control of cAMP and calmodulin-regulated kinases, whereas the skeletal isoform contains only one such site, suggesting that phosphorylation in cardiac muscle has a specific regulatory function. We isolated natural thick filaments from cardiac muscle and, using electron microscopy and optical diffraction, determined the effect of phosphorylation of MBP-C on cross bridges. The thickness of the filaments that had been treated with protein kinase A was increased where cross bridges were present. No change occurred in the central bare zone that is devoid of cross bridges. The intensity of the reflections along the 43-nm layer line, which is primarily due to the helical array of cross bridges, was increased, and the distance of the first peak reflection from the meridian along the 43-nm layer line was decreased. The results indicate that phosphorylation of MBP-C (i) extends the cross bridges from the backbone of the filament and (ii) increases their degree of order and/or alters their orientation. These changes could alter rate constants for attachment to and detachment from the thin filament and thereby modify force production in activated cardiac muscle.

1996

19/3,AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10510793 BIOSIS NO.: 199699131938
Tumor necrosis factor alpha promotes nuclear localization of cytokine-inducible CCAAT/enhancer binding protein isoforms in hepatocytes.
AUTHOR: Yin Ming; Yang Shi Qui; Lin Hui Zhi; Lane M Daniel; Chatterjee Subroto; Diehl Anna Mae(a)
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JOURNAL: Journal of Biological Chemistry 271 (30):p17974-17978 1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatocytes were cultured in the presence of recombinant tumor necrosis factor (TNF) alpha or mutated TNF alpha peptides that specifically activate either p55 or p75 TNF receptors to determine if TNF alpha can activate cytokine-inducible CCAAT/enhancer binding protein (C/EBP) isoforms by post-transcriptional mechanisms that are initiated by TNF receptors. Within 5-10 min after treatment with any of these agents, nuclear concentrations of C/EBP beta and C/EBP delta double and remain 2-4-fold greater than control cultures for 30 min (p < 0.01). Consistent with these results, gel mobility shift assays demonstrate 3-fold increased nuclear C/EBP beta- and C/EBP delta-DNA binding activity in TNF alpha-treated cells, and immunocytochemistry confirms rapid redistribution of these C/EBP isoforms into the nucleus. In contrast, mRNA and whole cell protein concentrations of C/EBP beta and delta are not altered by TNF alpha exposure, and nuclear concentrations of another C/EBP isoform, C/EBP alpha, are decreased by 80%. This novel evidence that TNF alpha initiates post-transcriptional activation of cytokine-inducible C/EBP isoforms identifies a mechanism that enables hepatocytes to respond immediately to inflammatory stress.

1996

19/3,AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10469728 BIOSIS NO.: 199699090873
GADD153/CHOP, a DNA damage-inducible protein, reduced CAAT/enhancer binding protein activities and increased apoptosis in 32D cl3 myeloid cells.
AUTHOR: Friedman Alan D
AUTHOR ADDRESS: Johns Hopkins Oncol. Center, Room 3-109, 600 North Wolfe St., Baltimore, MD 21287**USA
JOURNAL: Cancer Research 56 (14):p3250-3256 1996
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: GADD153/CHOP is a DNA damage-inducible, nuclear leucine zipper protein that is capable of producing a G1-S arrest in fibroblastic cells and of dimerizing with and inhibiting CAAT/enhancer binding protein (C/EBP) activities. CHOP was induced in 32D cl3 myeloid cells exposed to methylmethane sulfonate (MMS), a DNA alkylating agent. The degree of induction was dependent upon the dose of MMS to which the cells were exposed. CHOP was not expressed, at least at similar levels, during 32D cl3 cell granulocytic differentiation or during their apoptosis upon growth factor withdrawal. High-level expression of exogenous CHOP in 32D cl3 cells markedly inhibited the trans-activation

activities of endogenous C/EBPs. These cells proliferated in IL-3, although low-level ongoing apoptosis not observed with control cells was detected. When these cultures were transferred to granulocyte colony-stimulating factor (G-CSF), the majority of the cells underwent apoptosis, although the levels of CHOP did not increase. Similarly, 32D cl3 cells %%%treated%% with doses of MMS sufficient to induce endogenous CHOP underwent apoptosis more rapidly when placed in G-CSF-containing, compared with interleukin 3 (IL-3)containing, medium. However, induction of CHOP by MMS was similar in IL-3 and in G-CSF. The heightened sensitivity of 32D cl3 cells to CHOP in G-CSF could result either from the loss of IL-3-specific signals or from increased expression of C/EBPs. Because myeloid leukemias express C/EBPa, induction of CHOP might contribute to their chemotherapy-induced apoptosis, and alterations in CHOP expression could contribute to their development of chemotherapy resistance.

%%1996%%

19/3,AB/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10465222 BIOSIS NO.: 199699086367
C/EBP-beta is a negative regulator of human papillomavirus type 11 in keratinocytes.
AUTHOR: Wang Hao; Liu Kai; Yuan Fang; Berdichevsky Lillian; Taichman Lorne
B; Auburn Karen(a)
AUTHOR ADDRESS: (a)Dep. Otolaryngology, 270-05 76th Ave., Long Island Jewish Med. Cent., New Hyde Park, NY 11040**USA
JOURNAL: Journal of Virology 70 (7):p4839-4844 %%%1996%%
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have evaluated the impact of the CCAAT enhancer-%%binding%% protein-%%(%%C%%/EBP) transcription factors on human papillomavirus type 11 (HPV11). C/EBP-beta is in nuclei of cultured foreskin keratinocytes and binds its consensus sequence in HPV11 DNA. We have used the novel approach of depleting the availability of C/EBPs in vivo using nuclease-resistant oligomers containing C/EBP DNA binding sites. In cultured foreskin keratinocytes containing replicating HPV11 DNA, levels of both HPV11 transcripts and HPV DNA increase after %%%treatment%% with oligomers containing the C/EBP-beta DNA binding motif. These results indicate that C/EBP-beta is a repressor for HPV11 in keratinocytes.

%%1996%%

19/3,AB/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10433764 BIOSIS NO.: 199699054909
Involvement of CCAAT/enhancer-binding protein and nuclear factor-kappa-B binding sites in interleukin-6 promoter inhibition by estrogens.
AUTHOR: Galien Rene; Evans Helen F; Garcia Teresa(a)
AUTHOR ADDRESS: (a)Roussel Uclaf, 102 Route Noisy, Romainville Cedex 93235 **France
JOURNAL: Molecular Endocrinology 10 (6):p713-722 %%%1996%%
ISSN: 0888-8809
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bone loss observed in postmenopausal women is clearly associated with a decrease in estrogen levels. Interleukin 6 (IL-6), a multifunctional cytokine involved in osteoclast differentiation, is

secreted by osteoblasts and appears to be a key molecule in the osteoporotic process. As previous reports have shown that the human IL-6 promoter is inhibited by estradiol, we investigated the mechanism of estradiol (E-2)-mediated IL-6 inhibition in human cells. Analysis of the IL-6 secretion as a function of time in osteoblastoma Saos-2 cells, using an IL-6 ELISA test, showed that a maximal E-2 inhibition of tumor necrosis factor-alpha (TNF-alpha) induction could be monitored between 2 and 24 h of %%%treatment%%. IL-6 inhibition was clearly estrogen agonist-specific in Saos-2 and MCF7 cells. Transient transfections of HeLa cells with a pIL-6/CAT plasmid and an estrogen receptor (human ER) expression vector, confirmed the role of the human ER in inhibition of the IL-6 promoter. Deletion and mutational analysis of the promoter highlighted the role of the -185/-60 region and showed that in both MCF7 and HeLa cells, the nuclear factor-IL 6 (NF-IL6) site cooperates with the nuclear factor-kappa-B (NF-kappa-B) motif to produce maximal induction by TNF-alpha, whereas the CCAAT/enhancer-%%binding%% protein-%%(%%C%%/EBP) site displayed different cooperative effects toward NF-kappa-B depending on the cell line used. In HeLa cells, but not in MCF7 cells, we defined an essential role for the C/EBP site by showing that the E-2 sensitivity was clearly dependent on its integrity. In these cell lines, the NF-kappa-B site mutation abrogated both the TNF-alpha and E-2- sensitivity of the construct.

%%1996%%

19/3,AB/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10433561 BIOSIS NO.: 199699054706
Alteration by 2,3,7,8-tetrachlorodibenzo-p-dioxin of CCAAT/enhancer binding protein correlates with suppression of adipocyte differentiation in 3T3-L1 cells.
AUTHOR: Liu Phillip C C; Phillips Marjorie A; Matsumura Fumio(a)
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JOURNAL: Molecular Pharmacology 49 (6):p989-997 %%%1996%%
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds elicit multiple effects on the function of adipose tissue and adipogenic cell lines, including the suppression of adipocyte differentiation. We began to examine the mechanism by which TCDD inhibits differentiation of the established preadipocyte cell line 3T3-L1. Examination of the expression of several early marker genes of preadipocyte differentiation through Northern blot analysis and of differentiation-dependent mitosis showed that TCDD did not interfere with the earliest known responses of preadipocytes to inducers of differentiation. Analysis of mRNA for three isoforms of the CCAAT/enhancer %%%binding%% protein-%%(%%C%%/EBP) revealed that TCDD (5 nM) selectively inhibited the induction of C/EBP-alpha mRNA but did not block the induction of C/EBP-beta and C/EBP-delta in response to differentiation inducers. The differentiation-dependent induction of PPAR-gamma mRNA was also blocked by TCDD. Immunoblot analysis with specific antibodies to each C/EBP isoform demonstrated that the levels of C/EBP-delta and C/EBP-beta protein were rapidly induced (by day 1) and then abrogated by day 4 and 8, respectively, in solvent-%%treated%% (control) cells. In TCDD-%%treated%% cells, however, the levels of C/EBP-beta and C/EBP-delta protein persisted at these time points. In contrast, C/EBP-alpha protein was markedly suppressed by TCDD in concordance with its level of RNA. Both translational products of C/EBP-alpha, p30 and p42, were dose-dependently decreased by TCDD. Gel shift analysis of nuclear extract binding to an oligonucleotide containing a C/EBP DNA recognition sequence revealed no difference between extracts from control and TCDD-%%treated%% cells in the binding pattern at day 2 of differentiation. At days 4 and 8, the band corresponding to the C/EBP-alpha/DNA complex

(as determined with supershift assays) was dramatically decreased in the %%%treated%%% extracts in comparison to control extracts. In contrast, a band corresponding to a C/EBP-beta/DNA complex was found to be enriched in the %%%treated%%% samples. These data indicate that suppression of differentiation in the 3T3-L1 preadipocyte cell line by TCDD occurs at a short but defined period, during the differentiation program, and involves altered regulation of C/EBP, including the inhibition of C/EBP-alpha.

%%1996%%

19/3,AB/19 (Item 19 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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10433476 BIOSIS NO.: 199699054621
Physical and functional association between GADD153 and CCAAT/enhancer-binding protein beta during cellular stress.
AUTHOR: Fawcett Timothy W; Eastman Helen B; Martindale Jennifer L; Holbrook Nikki J(a)
AUTHOR ADDRESS: (a)Gene Expression Aging Section, Natl. Inst. Aging, Gerontol. Res. Cent., 4940 Eastern Ave., Box 3**USA
JOURNAL: Journal of Biological Chemistry 271 (24):p14285-14289
%%1996%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: GADD153, a ubiquitously expressed member of the CCAAT/enhancer-%%binding%% protein%% (%%C%%/EBP) family is induced by a wide variety of growth-arresting and DNA-damaging agents. Functionally, GADD153 has been postulated to act as a dominant-negative regulator of C/EBPs. Therefore we sought to gain evidence for interactions between GADD153 and other C/EBPs during cellular responses to stress. In this report we have demonstrated that %%treatment%% of rat pheochromocytoma PC12 cells with sodium arsenite leads to enhanced expression of C/EBP-beta and GADD153 (growth arrest and DNA damage inducible gene 153) but not other C/EBPs. Coimmunoprecipitation experiments provided evidence for the formation of endogenous GADD153-C/EBP-beta complexes in arsenite-%%treated%%% cells. Additional experiments were performed to determine the role of such complexes in regulating GADD153 expression. Previous studies in our laboratory demonstrated that the GADD153 promoter contains a C/EBP binding site through which other C/EBPs interact to transactivate GADD153 expression in liver hepatoma cells. Here, we demonstrate that extracts prepared from arsenite-%%treated%%% PC12 cells likewise show increased amounts of factors capable of binding to the GADD153-C/EBP site and that these complexes are comprised at least in part of C/EBP-beta. Forced expression of C/EBP-beta was found to be capable of transactivating the GADD153 promoter in PC12 cells cotransfected with plasmids expressing a GADD153 reporter gene and C/EBP-beta protein. However, overexpression of GADD153 inhibited the transactivation of the GADD153 promoter by C/EBP-beta. These findings provide evidence for an autoregulatory loop in which stress-induced GADD153 feeds back to attenuate GADD153 expression during the cellular response to stress.

%%1996%%

19/3,AB/20 (Item 20 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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10246634 BIOSIS NO.: 199698701552
Role of the C terminus in antigen P1 surface localization in Streptococcus

mutans and two related cocci.
AUTHOR: Homonylo-McGavin Mary K; Lee Song F(a)
AUTHOR ADDRESS: (a)Dep. Appl. Oral Sci., Fac. Dent., Dalhousie Univ., Halifax, NS B3H 3J5**Canada
JOURNAL: Journal of Bacteriology 178 (3):p801-807 %%1996%%
ISSN: 0021-9193
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The C terminus of the major surface protein P1 from Streptococcus mutans is composed of a hydrophilic domain, an LPNTGV motif, a hydrophobic domain, and a charged tail. These features are shared by surface proteins from many gram-positive coccal bacteria. To investigate the role of the C-terminal domains in antigen P1 surface localization, full-length and truncated P1 gene constructs, which were expressed on the shuttle vector pDL276, were transformed into the P1-negative mutant S. mutans SM3352, Streptococcus gordonii DL-1 and Enterococcus faecalis UV202. Transformants were tested for expression of P1 by enzyme-linked immunosorbent assaying and Western blotting. The results showed that full-length P1 was expressed by transformants of all three bacteria and was localized on the cell surface. A fusion protein composed of the Staphylococcus aureus fibronectin %%binding%% protein%% terminus and the P1 protein N terminus was found to surface localize in S. mutans. Deletion of the entire C-terminal domains resulted in P1 being expressed in the culture supernatant. A P1 truncation, which carried only the hydrophilic domain at its C terminus, was found partially associated with the cell surface. This truncated P1 was readily removed from the isolated cell wall by hot sodium dodecyl sulfate-mercaptoethanol extraction. In contrast, the full-length P1 remained associated with the isolated cell wall after similar %%treatment%%, suggesting covalent linkages between the full-length P1 and the cell wall. The results described above showed that antigen P1 was anchored to the cell wall by its C-terminal domains probably via covalent linkages with the cell wall. The results also support a universal mechanism involving the C-terminal domains for protein surface localization among this group of gram-positive bacteria.

%%1996%%

19/3,AB/21 (Item 21 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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10224408 BIOSIS NO.: 199698679326
Transcriptional regulation of the CYP2B1 and CYP2B2 genes by C/EBP-related proteins.
AUTHOR: Luc Phuong-Van T; Adesnik Milton; Ganguly Sabya; Shaw Peter M(a)
AUTHOR ADDRESS: (a)PanVera Corporation, 545 Science Drive, Madison, WI 53711**USA
JOURNAL: Biochemical Pharmacology 51 (3):p345-356 %%1996%%
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytochrome P450 (CYP) 2B1 and 2B2 are encoded by two closely related genes, CYP2B1 and CYP2B2, that are expressed at low levels in adult rat liver but are induced markedly by the administration of the drug phenobarbital (PB) or other structurally unrelated hydrophobic compounds to animals. Very little is understood about the molecular mechanisms that control both basal and induced transcription of these genes. We have identified two liver specific DNase I hypersensitive sites associated with the CYP2B1 and CYP2B2 (CYP2B) genes. One site, which maps to a region in the 5'-flanking region between -2.2 and -2.3 kb, became more resistant to DNase I cleavage in nuclei from PB-%%treated%%% rats; the converse was true of the other hypersensitive site, which maps to the proximal promoter region between -0.05 and -0.15 kb. DNase I footprint analysis revealed three prominent and one weak footprinted regions in the

promoter region in the vicinity of the proximal hypersensitive site. Using competitor oligonucleotides, we determined that one footprinted region (FT2), between -42 and -66 bp, is likely to represent a binding site for CCAATT enhancer binding protein (C/EBP) family members. Indeed, bacterially expressed recombinant C/EBP- α bound at this site and formed a footprint pattern identical to the pattern observed with liver nuclear extract. In vitro transcription assays demonstrated that the FT2 site contributed strongly to promoter activity, since its mutation reduced transcription by 80%. Two other sites identified by footprint analysis (FT1 and FT3) are also required to maintain high basal transcription of CYP2B2 promoter constructs in an in vitro transcription assay. Transient transfection experiments confirmed the expectation that C/EBP- α could activate the 1.4 kb CYP2B2 promoter constructs, with mutation of the FT2 site impairing both basal transcription and transactivation by exogenous C/EBP- α .

1996

19/3,AB/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10188123 BIOSIS NO.: 199698643041
Binding of activated T cells to a specific receptor on human mononuclear phagocytes inhibits intracellular calcium signaling and monocyte-dependent proliferative responses.
AUTHOR: Hancock Wayne H(a); Grey Shane T; Hatt Lena; Akalin Enver; Orthner Carolyn; Sayegh Mohamed H; Salem Hatem H
AUTHOR ADDRESS: (a)Sandoz Cent. Immunobiol., New England Deaconess Hosp., Harvard Med. Sch., 99 Brookline Ave., Boston, USA
JOURNAL: Transplantation (Baltimore) 60 (12):p1525-1532
1995
ISSN: 0041-1337
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Upon activation, mononuclear phagocytes (M- ϕ) play key roles in the development of septic shock and multiple host immune responses, but details of the regulation of M- ϕ activation are little understood. We recently showed that the physiologic anticoagulant molecule, activated protein C (APC), blocks responses of human blood M- ϕ , alveolar M- ϕ , or THP-1 cells induced by LPS, IFN- γ , or PMA, including TNF- α production and down-regulation of several LPS binding-related proteins. We now report a possible mechanism of action through inhibition of the rapid intracellular calcium signaling that occurs at the onset of M- ϕ activation, and characterization of a specific M- ϕ receptor for APC. Flow cytometry studies using Fluo-3 showed that M- ϕ activation by Fc-receptor cross-linking or rIFN- γ caused a rapid increase in free intracellular calcium, a primary event in multiple signal transduction pathways, which was blocked by pretreatment with APC. Consistent with this, addition of APC inhibited PHA-induced T cell proliferation in a dose- and time-dependent manner. Peak suppression (70%) required addition of APC within the first hour of 72 hr cocultures of M- ϕ and lymphocytes, and proliferative responses were not restored by addition of IL-2 or TNF- α . Biochemical studies showed that 125I-labeled APC bound specifically to M- ϕ in a time-dependent and saturable manner. Scatchard analysis indicated there were 180,690 binding sites for APC per cell, which were of high affinity (Kd value of 12.9 nM). Binding of 125I-APC was doubled by activation of M- ϕ with LPS, and bound APC was not displaced by the zymogen, protein C (PC), or by enzymatically inactive (diisopropyl fluorophosphate- or PPACK-treated) APC, indicating an absolute requirement for the active site of APC in its binding to M- ϕ . APC binding was blocked by a polyclonal Ab to human PC/APC, but not by protein S, factor Va or Xa, or a polyclonal antithrombomodulin antibody. When 125I-APC was crosslinked to its receptor, immunoprecipitated and analyzed by SDS-PAGE under reducing conditions, a covalent complex (110-115 kD) of 125I-APC (62 kD) and its

receptor was seen. In addition, a MO membrane protein of 50-55 kD, as determined by SDS-PAGE, was affinity-purified using an APC-Affigel column, and confirmed by ligand binding. Taken together, our findings document the presence of a M- ϕ surface receptor for APC, which appears distinct from a recently described endothelial receptor for PC and APC, and which may be involved in the inhibitory effects of APC on activation of human M- ϕ , including M- ϕ -dependent T cell proliferation.

1995

19/3,AB/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10156425 BIOSIS NO.: 199698611343
Recombinant human soluble thrombomodulin reduces endotoxin-induced pulmonary vascular injury via protein C activation in rats.
AUTHOR: Uchida Mitsuhiro; Okajima Kenji(a); Murakami Kazunori; Nawa Katsuhiko; Okabe Hiroaki; Takatsuki Kiyoshi
AUTHOR ADDRESS: (a)Dep. Lab. Med., Kumamoto Univ. Med. Sch., Honjo 1-1-1, Kumamoto 860, Japan
JOURNAL: Thrombosis and Haemostasis 74 (5):p1265-1270
1995
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Adult respiratory distress syndrome (ARDS) is a serious complication of disseminated intravascular coagulation (DIC) or multiple organ failure. To determine whether recombinant soluble human thrombomodulin (rsTM) may be useful in treating ARDS due to sepsis, we investigated the effect of rsTM on lipopolysaccharide (LPS)-induced pulmonary vascular injury in rats. The intravenous administration of rsTM prevented the increase in pulmonary vascular permeability induced by LPS. Neither heparin Plus antithrombin III (AT III) nor dansyl Glu Gly Arg chloromethyl ketone-treated factor Xa (DEGR-Xa), a selective inhibitor of thrombin generation prevented LPS-induced vascular injury. The agents rsTM, heparin plus AT III, and DEGR-Xa all significantly inhibited the LPS-induced intravascular coagulation. Recombinant soluble TM pretreated with a monoclonal antibody (moAb) that inhibits protein C activation by rsTM did not prevent the LPS-induced vascular injury; in contrast, rsTM pretreated with a moAb that does not affect thrombin binding or protein C activation by rsTM prevented vascular injury. Administration of activated protein C (APC) also prevented vascular injury. LPS-induced pulmonary vascular injury was significantly reduced in rats with leukopenia induced by nitrogen mustard and by ONO-5046, a potent inhibitor of granulocyte elastase. Results suggest that rsTM prevents LPS-induced pulmonary vascular injury via protein C activation and that the APC-induced prevention of vascular injury is independent of its anticoagulant activity, but dependent on its ability to inhibit leukocyte activation.

1995

19/3,AB/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10070607 BIOSIS NO.: 199598525525
Induction of heme oxygenase-1 gene expression by lipopolysaccharide is mediated by AP-1 activation.
AUTHOR: Camhi Sharon L; Alam Jawed; Otterbein Leo; Sylvester Sherrie L; Choi Augustine M K(a)
AUTHOR ADDRESS: (a)Div. Pulmonary and Critical Care, Johns Hopkins Univ. Sch. Med., Ross Res. Building, Room 858, Baltimore, USA
JOURNAL: American Journal of Respiratory Cell and Molecular Biology 13 (4):p387-398
1995
ISSN: 1044-1549

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Gram-negative sepsis is the most common cause of the adult respiratory distress syndrome (ARDS). Lipopolysaccharide (LPS) when administered in vivo produces pathophysiologic changes similar to those seen in ARDS. The pathogenesis of these changes is mediated in part by oxidative stress. We demonstrate that LPS induces high mRNA levels of the stress-inducible gene heme oxygenase-1 (HO-1) in the rat lung. Increased HO-1 mRNA levels correlate with increased HO-1 protein and enzyme activity. Immunohistochemical analyses of lung tissues from rats treated with LPS reveal abundant HO-1 expression in inflammatory and bronchoalveolar epithelial cells. We further examined the molecular regulation of HO-1 gene expression after exposure of RAW 264.7 macrophage cells to LPS in vitro. These cells respond to LPS with increased HO-1 mRNA expression and HO-1 gene transcription. Transcriptional activation of the mouse HO-1 gene by LPS is mediated by a 5' distal enhancer fragment located approximately 4 kbp upstream from the transcription site. Electrophoretic mobility shift assays show increased activator protein-1 (AP-1) binding activity in RAW 264.7 cells after LPS treatment. Mutation of the AP-1 binding site in this enhancer fragment completely abolishes HO-1 gene activation while mutation of CCAAT/enhancer-binding protein (C/EBP) binding site exerts negligible effect, suggesting that the AP-1 family of transcription factors plays a critical role in regulating HO-1 gene activation following LPS treatment. Furthermore, upstream phosphorylation events modulate this AP-1-dependent expression of the HO-1 gene after LPS treatment.

1995

19/3,AB/25 (Item 25 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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10012764 BIOSIS NO.: 199598467682
Developmentally and hormonally regulated CCAAT/enhancer-binding protein isoforms influence beta-casein gene expression.
AUTHOR: Raught Brian(a); Liao Warren S-L; Rosen Jeffrey M(a)
AUTHOR ADDRESS: (a)Dep. Cell Biol., Baylor Coll. Med., Houston, TX 77030**
USA
JOURNAL: Molecular Endocrinology 9 (9):p1223-1232 1995
ISSN: 0888-8809
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A highly conserved CCAAT/enhancer-binding protein (C/EBP)-binding site centered around -134 relative to the transcription start site in the rat beta-casein gene promoter is capable of interacting specifically with recombinant and mammary gland C/EBP proteins. Western blot analysis indicates that C/EBP levels change dramatically throughout mammary gland development. C/EBP-alpha expression is barely detectable in mammary glands from virgin and pregnant animals but is expressed at high levels during lactation and at lower levels during involution. The expression of three C/EBP-beta isoforms (the liver-enriched activating proteins (LAPs); and the liver-enriched inhibiting protein (LIP)) is elevated throughout pregnancy, with LIP expression increasing more than 100-fold. Thus, during pregnancy, a low LAP/LIP ratio (1:5) is maintained. C/EBP-beta expression decreases at parturition, with LIP diminishing to levels observed in the virgin gland. Therefore, during lactation a more than 100-fold increase in the LAP/LIP ratio is observed. Treatment of the HC11 mammary epithelial cell line with hydrocortisone results in a 10- to 20-fold inhibition of LIP expression, with only minor changes in LAP levels. Therefore, glucocorticoids may impinge upon beta-casein gene expression by altering the ratio of the inhibitory to the activating isoforms of C/EBP-beta. Several previously defined casein gene promoter regions capable of

conferring hormone and extracellular matrix inducibility to reporter genes in mammary cells are suggested to be composite response elements, containing putative binding sites for the same set of hormonally and developmentally regulated factors: C/EBP, MGF/Stat5, and the glucocorticoid receptor.

1995

19/3,AB/26 (Item 26 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09734314 BIOSIS NO.: 199598189232
Expression of the liver-enriched transcription factors C/EBP-alpha, C/EBP-beta, HNF-1, and HNF-4 in preneoplastic nodules and hepatocellular carcinoma in rat liver.
AUTHOR: Flodby Per; Liao De-Zhong; Blanck Agneta; Xanthopoulos Kleantis G
H: Hallstrom Inger Porsch(a)
AUTHOR ADDRESS: (a)Dep. Med. Nutrition, Huddinge Univ. Hosp., F60 NOVUM,
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JOURNAL: Molecular Carcinogenesis 12 (2):p103-109 1995
ISSN: 0899-1987
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The expression patterns of the liver-enriched transcription factors CCAAT/enhancer-binding protein (C/EBP) alpha and beta and hepatocyte nuclear factor (HNF)-1 and HNF-4 were studied in liver nodules and hepatocellular carcinomas from male rats treated according to the resistant hepatocyte (RH) model. C/EBP-alpha expression was lower at the transcriptional, mRNA, and protein levels in persistent nodules than in the respective surrounding livers. Expression was further decreased in the tumors. Transcriptional downregulation of C/EBP-alpha gene expression was observed already in very early nodules, isolated 3 wk after partial hepatectomy in the RH model. However, no detectable changes were observed in preneoplastic nodules in the transcription or in steady-state mRNA levels of C/EBP-beta, HNF-1, and HNF-4. A slight decrease in C/EBP-beta protein and a more pronounced attenuation of HNF-1 and HNF-4 levels was observed in nodules, being 67%, 37%, and 46% of the levels in the corresponding surrounding livers, respectively. In conclusion, differential regulation of several transcription factors that are associated with the maintenance of the differentiated state of the hepatocytes was observed in preneoplastic and neoplastic liver lesions. This could have an impact on the regulation of a wide array of genes during liver carcinogenesis. Furthermore, the attenuation of C/EBP-alpha expression, regarded as a negative growth regulator, could contribute to the proliferative advantage of nodules during liver carcinogenesis.

1995

19/3,AB/27 (Item 27 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09666743 BIOSIS NO.: 199598121661
Insulin regulates transcription of the CCAAT/Enhancer-binding protein (C/EBP) alpha, beta, and delta genes in fully-differentiated 3T3-L1 adipocytes.
AUTHOR: MacDougald Ormond A; Cornelius Peter; Liu Raymond; Lane M Daniel(a)
AUTHOR ADDRESS: (a)Dep. Biol. Chem., Johns Hopkins Univ., Sch. Med., 725 N.
Wolfe St., Baltimore, MD 21205**USA
JOURNAL: Journal of Biological Chemistry 270 (2):p647-654
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of insulin on expression of CCAAT/enhancer
binding protein (C/EBP) alpha, beta,
and delta was
investigated in fully-differentiated 3T3-L1 adipocytes.

Treatment of
adipocytes with insulin stimulated rapid dephosphorylation of
C/EBP-alpha, and repressed the expression of C/EBP-alpha within 2-4 h,
with a 90% suppression occurring at 24 h. While insulin induced
expression of C/EBP-beta and C/EBP-delta within 1 h and caused a 20-fold increase by 4 h, expression returned to nearly pretreatment
levels by 24 h. The insulin concentration dependence of these effects was
consistent with involvement of the insulin receptor. Gel shift analysis
revealed that 6 h of insulin treatment decreased the binding of
nuclear C/EBP-alpha while increasing binding of nuclear C/EBP-beta and
C/EBP-delta. The reciprocal effects of insulin on the steady-state levels
of C/EBP transcription factors can be accounted for kinetically and
quantitatively by changes in their mRNA levels, which can be accounted
for by effects on gene transcription. The effects of insulin on adipocyte
gene transcription (e.g. GLUT4) may be mediated, at least in part, by
down-regulation of C/EBP-alpha and/or its dephosphorylation.

1995

19/3,AB/28 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09641486 BIOSIS NO.: 199598096404
Hepatic CCAAT/enhancer binding protein (C/EBP) alpha and
C/EBP-beta expression changes with riboflavin deficiency, diet
restriction and starvation in rats.
AUTHOR: Chapin Rebecca B; Brady Paul S; Barke Roderick A; Brady
Linda J(a)
AUTHOR ADDRESS: (a)Dep. Food Sci. Nutr., Univ. Minn., St. Paul, MN
55108**
USA
JOURNAL: Journal of Nutrition 124 (12):p2365-2375 1994
ISSN: 0022-3166
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To study the role of nuclear regulatory proteins in mediating
dietary effects, hepatic CCAAT/enhancer binding protein (C/EBP) alpha and
C/EBP-beta (C/EBP), mRNA and transcription rate were measured for
C/EBP-alpha
and C/EBP-beta in nutritional states that profoundly alter energy
metabolism and growth. Weanling male Sprague-Dawley rats were fed
riboflavin-sufficient (R+) or deficient (R-) diets for 4 wk. A
diet-restricted, pair-fed (RP) group was maintained concurrently, because
riboflavin-deficient rats voluntarily decrease food consumption by approx
50% compared with controls. Half of each group was deprived of food for
48 h. The 4-wk treatment altered hepatic levels of both proteins (P

0.05). C/EBP-alpha protein levels were increased approx twofold by diet
restriction. C/EBP-beta protein levels were increased nearly threefold by
riboflavin deficiency. Starvation had no significant effect on the
expression of either protein. We investigated the mechanism responsible
for increased protein by measuring steady-state mRNA levels and
transcription rates for C/EBP-alpha and C/EBP-beta. In both isoforms,
increases in mRNA were parallel to increases in transcription rates. The
nutrient-induced changes in protein, mRNA and transcription rates could
not be attributed only to alterations in serum glucagon or insulin
concentrations. We conclude that 1) C/EBP-alpha and C/EBP-beta
expression
responds to diet but may involve different dietary signals for diet
restriction vs. riboflavin deficiency; 2) the dietary regulation of
C/EBP-alpha and C/EBP-beta expression seems to be controlled in part at
the level of gene transcription; and 3) C/EBP-alpha and C/EBP-beta
nuclear proteins, by virtue of their increased quantities, may
participate in regulating altered energy metabolism and growth by
influencing hepatic transcription of key metabolic enzymes.

1994

19/3,AB/29 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09544469 BIOSIS NO.: 199497552839
Multiple elements within the 5' distal enhancer of the mouse heme
oxygenase-1 gene mediate induction by heavy metals.
AUTHOR: Alam Jawed
AUTHOR ADDRESS: Dep. Mol. Genetics, Alton Ochsner Med.
Foundation, 1516
Jefferson Highway, New Orleans, LA 70121**USA
JOURNAL: Journal of Biological Chemistry 269 (40):p25049-25056
1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A 268-base pair 5' distal fragment, SX2, which mediates basal
level and inducer-dependent activation of the mouse heme oxygenase-1
gene, contains two activator protein-1 (AP-1) binding sites (Alam, J.,
and Zhining, D. (1992) J. Biol. Chem. 267,21894-21900). Mutation of both
AP-1 binding elements diminishes (by 50-70%), but does not abolish, the
enhancer activity of SX2 in transient expression assays, suggesting that
other sequences contribute to enhancer function. Directly upstream of the
AP-1 binding sites are two copies of a sequence motif, TGAGGAAAT,
which
resemble elements found in cellular and viral genes that are known to
interact with the CCAAT/enhancer binding protein (C/EBP) family of transcription factors. These SX2 sequences bind
specifically to liver-enriched, heat-stable nuclear proteins and confer
C/EBP alpha-dependent transactivation of the heterologous chloamphenicol
acetyltransferase (CAT) gene. Site-directed mutagenesis of these 9-base
pair elements abolishes protein binding and transactivation, establishing
these sequences as functional C/EBP binding sites. Stably transfected
SX2/CAT fusion genes are induced between 37- and 44-fold in mouse
hepatoma, Hepa, cells and between 52- and 111-fold in mouse fibroblast
L929 cells in response to CdCl-2 treatment. Subfragments of
SX2
lacking the AP-1 binding elements do not mediate cadmium-dependent
activation of the CAT gene, whereas subfragments containing the AP-1
binding elements, but lacking the C/EBP binding sites, exhibit only
partial transcriptional activity. Site-directed mutagenesis of one or
more of the C/EBP and AP-1 binding sites indicates that each of them
elements is required for optimal activity of the SX2 enhancer fragment.
The AP-1 binding elements, however, appear to be more important for
induction as constructs containing multiple copies of either of the AP-1
binding elements, but not the C/EBP binding sequences, are readily
activated by CdCl-2. Treatment of Hepa cells with cadmium or
heme
does not alter the nuclear concentration of AP-1 or C/EBP binding
activity.

1994

19/3,AB/30 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09409800 BIOSIS NO.: 199497418170
Induction of GADD153, A CCAAT/Enhancer binding protein (C/EBP)-related Gene, during the Acute Phase Response in Rats: Evidence for
the involvement of C/EBPs in regulating its expression.
AUTHOR: Sylvester Sherrie; Ap Rhys Colette M J; Luethy-Martindale
Jennifer
D; Holbrook Nikki J(a)
AUTHOR ADDRESS: (a)Sect. Gene Expression Aging, Gerontol. Res.
Cent., Natl.
Inst. Aging, Baltimore, MD 21224**USA
JOURNAL: Journal of Biological Chemistry 269 (31):p20119-20125
1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CCAAT/enhancer-binding proteins (C/EBPs) comprise a homologous group of transcriptional regulators that control liver and fat differentiation and are involved in regulating the expression of acute phase reactants during the host response to inflammation. GADD153, a unique member of the C/EBP family, has been proposed to act as a dominant negative inhibitor of other C/EBPs, but little is known about its expression in liver or its role in the processes described above. We have examined its expression during the acute phase response (APR) and have shown that like C/EBP-beta and C/EBP-delta, GADD153 mRNA is markedly induced in livers of rats treated with lipopolysaccharide to initiate the APR. Interestingly, its induction is temporally delayed relative to that of C/EBP-beta and C/EBP-delta but is similar to that of acute phase reactants shown to be regulated by C/EBPs. Footprint analysis of the GADD153 promoter showed binding of proteins in liver extracts of both untreated and lipopolysaccharide-injected rats to a putative C/EBP regulatory site. Gel shift analysis showed that although present constitutively, binding activity was increased in extracts from lipopolysaccharide-treated animals. Both C/EBP-alpha and C/EBP-beta were shown to contribute to the binding activity with the contribution by C/EBP-beta increasing during the APR. Support for the functional role of this C/EBP-binding site and its interaction with C/EBPs in regulating GADD153 expression was obtained with cultured HepG2 hepatoma cells in which overexpression of C/EBP-beta was found to transactivate expression of a plasmid containing the GADD153 promoter linked to a reporter gene. These findings suggest that the GADD153 gene is itself regulated by C/EBPs during the host response to inflammation and that GADD153 is likely to contribute to the regulation of other genes whose expression is altered during the APR.

1994

19/3,AB/31 (Item 31 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09405887 BIOSIS NO.: 199497414257
Glucocorticoids reciprocally regulate expression of the CCAAT/enhancer-binding protein alpha and delta genes in 3T3-L1 adipocytes and white adipose tissue.
AUTHOR: MacDougald Ommond A; Comelius Peter; Lin Fang-Tsyr; Chen Sylvia S; Lane M Daniel(a)
AUTHOR ADDRESS: (a)Dep. Biological Chemistry, Johns Hopkins Univ. Sch. Med., Baltimore, MD 21205**USA
JOURNAL: Journal of Biological Chemistry 269 (29):p19041-19047
1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glucocorticoid agonists, i.e. dexamethasone or triamcinolone acetonide, rapidly induce expression of CCAAT/enhancer-binding protein (C/EBP) delta and repress expression of C/EBP-alpha in fully differentiated 3T3-L1 adipocytes. Within 30 min of glucocorticoid treatment, the cellular level of C/EBP-delta rises dramatically, increasing 100-fold within 6 h. Concurrently, the level of C/EBP-alpha decreases, reaching a minimum within 4 h. The dexamethasone concentration dependence and steroid specificity of these responses suggest that both processes are mediated by the glucocorticoid receptor. The reciprocal effects of dexamethasone on the steady-state levels of C/EBP-alpha and C/EBP-delta can be accounted for kinetically and quantitatively by changes in their mRNA levels and by the transcription rates of their respective genes. The glucocorticoid-induced changes in expression of the C/EBP isoforms are correlated with the transcriptional activation of the SCD1 gene, an adipocyte gene known to be transactivated by C/EBP isoforms. Glucocorticoids also regulate expression of the C/EBP isoforms in vivo. Within 4 h of administration of dexamethasone or triamcinolone acetonide to adult rats, expression of C/EBP-delta is induced in white adipose tissue while expression of

C/EBP-alpha is repressed. Like the response in 3T3-L1 adipocytes, the effects of dexamethasone on C/EBP-alpha in white adipose tissue are rapid and transient.

1994

19/3,AB/32 (Item 32 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09307646 BIOSIS NO.: 199497316016
Binding of urinary protein C inhibitor to cultured human epithelial kidney tumor cells (TCL-598): The role of glycosaminoglycans present on the luminal cell surface.
AUTHOR: Priglinger Ute; Geiger Margarethe(a); Bielek Edith; Vanyek Erika; Binder Bernd R
AUTHOR ADDRESS: (a)Lab. Clinical Experimental Physiol., Dep. Med. Physiol., Schwarzschanerstrasse 17, A1090 Vienna**Austria
JOURNAL: Journal of Biological Chemistry 269 (20):p14705-14710
1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Binding of urinary protein C inhibitor (PCI) to cultured human epithelial kidney tumor cells (TCL-598) was studied. Binding was dose-dependent, time-dependent, and saturable. Heparin interfered in a dose-dependent way with PCI binding to TCL-598 as did heparan sulfate and to a lesser degree also dermatan sulfate. Pretreatment of TCL-598 with protamine sulfate inhibited subsequent binding of PCI in a dose-dependent manner and at 100 µg/ml protamine sulfate reduced binding of PCI to 10% of the control. Binding of 125I-PCI was specific, and bound 125I-PCI was recovered from the cells by heparin treatment or detached together with intact cells by EDTA treatment, migrated on sodium dodecyl sulfate-polyacrylamide gel electrophoresis with the same mobility ($M_r = 57,000$) as unbound 125I-PCI. Furthermore, cell-bound PCI was functionally active as judged from its ability to inhibit the amidolytic activity of urokinase, and its inhibitory activity was stimulated approx 3-4-fold as compared to fluid-phase PCI. Immunogold electron microscopy revealed that PCI-antigen presented to the cells from the luminal side bound exclusively to that surface in native as well as in prefixed cells. This binding of PCI was abolished in the presence of heparin (50 µg/ml) and after pretreatment of the cells either with protamine sulfate (400 µg/ml) or with heparinase III (0.5 unit/ml). A slight decrease in PCI binding was seen after pretreatment of the cells with chondroitinase ABC and chondroitinase AC. In contrast, binding of PCI to extracellular matrices of TCL-598 was decreased to approx 70% after chondroitinase ABC treatment of the extracellular matrices, whereas both heparinase III or chondroitinase AC treatment only reduced matrix-bound PCI to approx 95%. These data suggest that heparan sulfate-containing proteoglycans are predominantly involved in binding of PCI to the luminal side of TCL-598, while dermatan sulfate-containing proteoglycans, the overall predominant PCI-binding proteoglycans in TCL extracts, are responsible for PCI binding to the extracellular matrix. Heparan sulfate, however, exposed to an environment containing PCI under physiological conditions, might localize PCI and modulate its target enzyme specificity in vivo.

1994

19/3,AB/33 (Item 33 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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09304383 BIOSIS NO.: 199497312753
Serum amyloid A gene expression under acute-phase conditions involves participation of inducible C/EBP-beta and C/EBP-delta and their

activation by phosphorylation.
 AUTHOR: Ray Alpina; Ray Bimal K(a)
 AUTHOR ADDRESS: (a)Dep. Vet Microbiol., University Missouri, 20
 Conway
 Hall, Columbia, MO 65211**USA
 JOURNAL: Molecular and Cellular Biology 14 (6):p4324-4332
 %%%1994%%
 ISSN: 0270-7306
 DOCUMENT TYPE: Article
 RECORD TYPE: Abstract
 LANGUAGE: English

ABSTRACT: Serum amyloid A (SAA) is a plasma protein whose synthesis is markedly increased in the liver during the inflammatory process. Previous analysis of SAA promoter function implicated the involvement of the CCAAT/enhancer-%%binding%% protein%% in controlling this process. In this study, using antibodies against three C/EBP isoforms in DNA-binding and Western blot (immunoblot) assays, we found that in response to inflammatory signals, both C/EBP-delta and C/EBP-beta are induced and that their interactions with the SAA promoter element are necessary for the increased SAA gene expression. Cotransfections of liver cells with an SAA promoter-linked reporter chloramphenicol acetyltransferase gene and murine sarcoma virus-expressed C/EBP-delta or C/EBP-beta confirm such phenomena. The increased transactivating ability in the presence of the cellular phosphatase inhibitors okadaic acid and sodium orthovanadate, coupled with the observation that dephosphorylation severely inhibits the DNA-binding ability in vitro, implicates a role of phosphorylation in the regulation of the activities of the C/EBP-delta isoform. Consistent with these findings, we have detected higher levels of DNA-binding activity of C/EBP-delta prepared from cells %%%treated%% with phosphatase inhibitors. We also present evidence that C/EBP-delta is a phosphoprotein. These results suggest that C/EBP-delta is regulated by phosphorylation and, in conjunction with C/EBP-beta, is one of the major proteins responsible for the increased transcription of the SAA gene in response to inflammatory stimuli.

%%1994%%

19/3,AB/34 (Item 34 from file: 5)
 DIALOG(R)File 5: Biosis Previews(R)
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08853036 BIOSIS NO.: 199396004537
 Participation of the transcription factor C/EBP-delta in the acute-phase regulation of the human gene for complement component C3.
 AUTHOR: Juan Todd S-C; Wilson Deborah R; Wilde Margaret D; Darlington Gretchen J(a)
 AUTHOR ADDRESS: (a)Dep. Pathol., Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030**USA
 JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 90 (7):p2584-2588 %%%1993%%
 ISSN: 0027-8424
 DOCUMENT TYPE: Article
 RECORD TYPE: Abstract
 LANGUAGE: English

ABSTRACT: C3, the third component of complement, is critical in the host immune response in that it is involved in both the classical and alternative pathways of complement activation. We have previously shown that a region (bp -127 to -70) within the C3 promoter is indispensable for conferring interleukin 1 (IL-1) responsiveness to this gene. A sequence comparison reveals two CCAAT/enhancer %%binding%% protein%% (%%C%%/EBP) consensus sequences, basic DNA binding region and leucine zippers 1 and 2 (bZIP1 and bZIP2), within this region. Site-directed mutagenesis of the more 3' C/EBP site (bZIP1) in the C3 promoter significantly reduced the basal level of expression and the IL-1 responsiveness of the reporter gene, whereas mutation in the second, more 5', C/EBP consensus sequence (bZIP2) had a minimal effect on basal expression and IL-1 inducibility. Electrophoretic-mobility-shift assays, with and without antibodies to the different C/EBP proteins that "supershift" protein-DNA complexes, demonstrated that proteins binding at the 3' C/EBP site formed several complexes. Antibodies to C/EBP-alpha

supershifted the majority of complexes formed with extracts from control cells. Antibodies directed against C/EBP-delta supershifted the major IL-1-inducible complexes. Western immunoblot analyses showed that the level of C/EBP-delta protein was increased dramatically in the nuclei of Hep 3B2 cells after 4 h of IL-1 %%%treatment%%. When Hep 3B2 cells were cotransfected with a C/EBP-delta expression vector and a construct with a C3 promoter and a reporter gene, C/EBP-delta was able to transactivate the C3 promoter in an IL-1-responsive manner. The data strongly suggest that C/EBP-delta is the major protein responsible for regulating the acute-phase expression of the human C3 gene.

%%1993%%

19/3,AB/35 (Item 35 from file: 5)
 DIALOG(R)File 5: Biosis Previews(R)
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08424528 BIOSIS NO.: 000094131732
 CALCIUM IONOPHORE A23187 INDUCES EXPRESSION OF THE GROWTH ARREST AND DNA DAMAGE INDUCIBLE CCAAT-ENHANCER-%%binding%% PROTEIN%% C%%/EBP-RELATED GENE GADD153 CALCIUM INCREASES TRANSCRIPTIONAL ACTIVITY AND MRNA STABILITY
 AUTHOR: BARTLETT J D; LUETHY J D; CARLSON S G; SOLLOTT S J; HOLBROOK N J
 AUTHOR ADDRESS: LABORATORY MOLECULAR GENETICS, NATIONAL INSTITUTE AGING, BALTIMORE, MD. 21224.
 JOURNAL: J BIOL CHEM 267 (28). 1992. 20465-20470. %%%1992%%
 FULL JOURNAL NAME: Journal of Biological Chemistry
 CODEN: JBCHA
 RECORD TYPE: Abstract
 LANGUAGE: ENGLISH

ABSTRACT: gadd153 is a CCAAT/enhancer-%%binding%% protein%% (%%C%%/EBP)-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Ca2+ might play a role in regulating expression of gadd153. We have demonstrated that %%%treatment%% of HeLa cells with the calcium ionophores A23187 and ionomycin leads to the induction of gadd153 mRNA. The induction was rapid; increases in mRNA were detected by 90 min of %%%treatment%%, and near maximum levels were achieved within 5-h exposure to A23187. Elevated mRNA levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression. Buffering intracellular and extracellular Ca2+ by combined %%%treatment%% with BAPTA-AM (acetoxymethyl ester form of bis(aminophenoxy)ethane N,N'-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA by A23187. In addition, these %%%treatments%% prevented the induction of gadd153 mRNA in response to the DNA damaging agent methyl methanesulfonate. We conclude that intracellular Ca2+ plays a role in regulating gadd153 expression. More specifically, Ca2+ likely plays a role in the induction of gadd153 mRNA following DNA damage.

%%1992%%

19/3,AB/36 (Item 36 from file: 5)
 DIALOG(R)File 5: Biosis Previews(R)
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08422530 BIOSIS NO.: 000094129734
 ROLE OF CAAT-ENHANCER BINDING PROTEIN ISOFORMS IN THE CYTOKINE REGULATION OF ACUTE-PHASE PLASMA PROTEIN GENES
 AUTHOR: BAUMANN H; MORELLA K K; CAMPOS S P; CAO Z; JAHREIS G P

AUTHOR ADDRESS: DEP. MOLECULAR CELLULAR BIOL.,
ROSWELL PARK CANCER INST.,
BUFFALO, NEW YORK 14263.
JOURNAL: J BIOL CHEM 267 (27). 1992. 19744-19751. %%%1992%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Rat hepatic cells respond to interleukin (IL) -1, IL-6, and dexamethasone %%%treatment%% by increasing the transcription rate of acute-phase plasma protein genes. The same conditions lead to changes in the expression of CAAT-enhancer %%%binding%% %%%protein%% (%%%C%%/EBP) isoforms which are specific to the hepatic cell line. To identify the relationship between C/EBP isoforms and acute-phase protein gene activation, the hormone-specific expression of C/EBP.alpha., .beta., and .delta. was determined in H-35 and HTC cells and was compared to acute-phase liver. C/EBP.beta. was found to be the principal isoform in hepatoma cells and to be strongly stimulated by cytokines and dexamethasone in H-35 cells. Transactivating functions were observed for all three C/EBP isoforms by cotransfection of CAT gene reporter constructs containing cytokine and glucocorticoid response elements of acute-phase protein genes and expression plasmids for mouse C/EBP.alpha., .beta. and .delta. into rat and human hepatoma cells. The degree of C/EBP-mediated transactivation was, however, extremely variable among the different regulatory elements. Transcription run-on reactions with nuclei from transiently transfected H-35 indicated that cotransfected C/EBP.beta. increases basal expression of reporter gene constructs as well as the dexamethasone-mediated stimulation of constructs containing the glucocorticoid response elements of the rat .alpha.1-acid glycoprotein gene, but did not accelerate or enhance hormone-dependent transcription activation of reporter gene plasmids containing the IL-6 regulatory element of the .beta.-fibrinogen gene. Activation of the reporter gene constructs appeared to be temporally and quantitatively correlated with the amount of nuclear C/EBP as determined by two-dimensional Western and Southwestern blot analyses.

%%1992%%

19/3,AB/37 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0833333 BIOSIS NO.: 000094084581
CCAAT-ENHANCER BINDING PROTEIN EXPRESSION IS RAPIDLY
EXTINGUISHED IN TAI
ADIPOCYTE CELLS %%%TREATED%% WITH TUMOR NECROSIS
FACTOR
AUTHOR: WILLIAMS P M; CHANG D J; DANESCH U; RINGOLD G M;
HELLER R A
AUTHOR ADDRESS: INST. CANCER AND DEV. BIOL., SYNTAX
RES., 3401 HILLVIEW
AVE., PALO ALTO, CALIF. 94303.
JOURNAL: MOL ENDOCRINOL 6 (7). 1992. 1135-1141. %%%1992%%
FULL JOURNAL NAME: Molecular Endocrinology
CODEN: MOENE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tumor necrosis factor (TNF) has been shown to have diverse effects on a wide variety of cell types. In the mouse adipogenic TAI cell line, TNF completely abolishes differentiation and reverts fully differentiated fat cells into fibroblasts. This block in differentiation and its reversal is due to the rapid reduction in the expression of adipose-specific genes. This study reports that the transcription factor, CCAAT/enhancer %%%binding%% %%%protein%% (%%%C%%/EBP), previously reported to promote the differentiation of 3T3-L1 adipocytes, is expressed in TAI cells. During their growth in culture, the levels of C/EBP, as evidenced by its cellular levels of specific mRNA, protein, and DNA binding activity, increase dramatically when cell reach confluence and proceed to differentiate. Addition of TNF to cultured preadipocytes of fully differentiated adipocytes rapidly reduces C/EBP levels and is accompanied by the decrease in expression of adipose-specific genes. C/EBP binding sites occur in several adipose-specific genes, and here it

is demonstrated that its presence in a novel adipose-specific gene, Clone 47, also referred to as FSP27, may be responsible for the strong down-regulation of the expression of the Clone 47 (FSP27) promoter-linked chloramphenicol acetyl transferase gene by TNF. This study proposes that the loss of C/EBP in response to TNF %%%treatment%% may in part explain the loss of the adipocyte differentiated state.

%%1992%%

19/3,AB/38 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08135523 BIOSIS NO.: 000093122671
DIFFERENTIAL EXPRESSION OF THREE C-EBP ISOFORMS IN
MULTIPLE TISSUES DURING
THE ACUTE PHASE RESPONSE
AUTHOR: ALAM T; AN M R; PAPACONSTANTINO J
AUTHOR ADDRESS: DEP. HUMAN BIOL. CHEM. GENETICS, 613
BASIC SCI. BUILDING,
RT. F43, UNIV. TEXAS MED. BRANCH, GALVESTON, TEXAS 77550.
JOURNAL: J BIOL CHEM 267 (8). 1992. 5021-5024. %%%1992%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Eucaryotic organisms possess natural defense processes triggered by stress factors such as injury, infection, and inflammation. The acute phase response is an early defense mechanism during which striking changes in protein synthesis occur in the liver and other tissues. The altered expression of many acute phase protein genes is at the transcriptional level. Some of these genes have DNA binding sites for the CCAAT/enhancer %%%binding%% %%%protein%% (%%%C%%/EBP) family of transcription factors. We report here that in vivo expression of three isoforms of C/EBP is dramatically changed during the acute phase response. The steady-state mRNA levels of C/EBP.alpha. decreased significantly in the liver, lung and fat tissues of lipopolysaccharide (LPS)-%%treated%% mice; moreover, nuclear run-off transcription assays indicated a decrease in the rate of C/EBP.alpha. gene transcription in isolated liver nuclei. The steady-state levels of C/EBP.beta. and new isoform, C/EBP.delta., were dramatically increased in many tissues within 4 h following LPS %%%treatment%%. The rates of transcription of these two genes were only minimally altered in liver but significantly increased in kidney nuclei isolated from stimulated animals. Thus, the C/EBP isoforms exhibit differential mechanisms in their responses to LPS in various tissues and are likely to play an important role in mediating the transcriptional activation of genes involved in the acute phase response.

%%1992%%

19/3,AB/39 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08016255 BIOSIS NO.: 000093061178
TUMOR NECROSIS FACTOR-INDUCED REVERSAL OF ADIPOCYTIC
PHENOTYPE OF 3T3-L1
CELLS IS PRECEDED BY A LOSS OF NUCLEAR
CCAAT-ENHANCER %%%BINDING%%
%%PROTEIN%% %%%C%%/EBP
AUTHOR: RON D; BRASIER A R; MCGHEE R E JR; HABENER J F
AUTHOR ADDRESS: LAB. MOL. ENDOCRINOL., MASS. GEN. HOSP.,
HOWARD HUGHES MED.
INST., HARVARD MED. SCH., BOSTON, MASS. 02114.
JOURNAL: J CLIN INVEST 89 (1). 1992. 223-233. %%%1992%%
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tumor necrosis factor (TNF)- α treated 3T3-L1 adipocytes were used as a model for studying the effects of systemic inflammation of adipose tissue. Lipopolysaccharide treatment of monocyte-conditioned medium or recombinant human TNF α induced morphological dedifferentiation of the adipocytes and led to loss of adipocyte specific gene expression. Gel shift, Southwestern and Western immunoblot analysis demonstrated that dedifferentiation was preceded by a decrease in DNA binding activity and protein level of the transcription factor CCAAT/enhancer binding protein (C/EBP). Liver activating protein, a related protein that binds identical DNA sequences, increased during cytokine treatment. Both proteins activate specific enhancer elements located in the promoter region of many genes whose transcription is altered during systemic inflammation. Pulse-chase labeling followed by immunoprecipitation demonstrated that C/EBP is a rapidly turning over protein in adipocytes and that cytokine treatment led to a specific, time dependent decrease in its rate of synthesis. Because C/EBP binding sites have been shown to play an important role in regulating the expression of genes involved in adipocyte metabolism, we propose that the TNF-induced changes in the complement of transcription factors binding those sites may be important in the pathogenesis of inflammation-induced atrophy of adipose tissue.

1992

19/3,AB/40 (Item 40 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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07996770 BIOSIS NO.: 000093052443
A PHOSPHORYLATION SITE LOCATED IN THE AMINO-TERMINAL DOMAIN OF C-MYC INCREASES TRANSACTIVATION OF GENE EXPRESSION
AUTHOR: SETH A; ALVAREZ E; GUPTA S; DAVIS R J
AUTHOR ADDRESS: HOWARD HUGHES MEDICAL INSTITUTE, PROGRAM MOLECULAR MEDICINE, UNIVERSITY MASSACHUSETTS MEDICAL SCHOOL, 373 PLANTATION ST., WORCESTER, MASS. 01605.
JOURNAL: J BIOL CHEM 266 (35). 1991. 23521-23524. 1991
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The c-myc gene encodes a sequence-specific DNA-binding protein (c-Myc) that forms leucine zipper complexes and can act as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Ser62 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I. C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R. J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34cdc2. We report that serum treatment of cells results in a marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutant at the site of growth factor-stimulated phosphorylation (Ser62) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

1991

19/3,AB/41 (Item 41 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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07659780 BIOSIS NO.: 000092017201
NATURAL ANTICOAGULANTS IN SYSTEMIC LUPUS ERYTHEMATOSUS DEFICIENCY OF

PROTEIN S BOUND TO C4BP ASSOCIATED WITH RECENT HISTORY OF VENOUS THROMBOSES ANTIPHOSPHOLIPID ANTIBODIES AND THE ANTIPHOSPHOLIPID SYNDROME
AUTHOR: RUIZ-ARGUELLES G J; RUIZ-ARGUELLES A; ALARCON-SEGOVIA D; DRENKARD C ; VILLA A; CABIEDES J; PRESNO-BERNAL M; DELEZE M; ORTIZ-LOPEZ R; VAZQUEZ PRADO J
AUTHOR ADDRESS: DEP. IMMUNOL. AND RHEUMATOL., INST. NACL. NUTRICION SALVADOR ZUBIRAN, VASCO DE QUIROGA 15, 1400 MEXICO DF, MEXICO.
JOURNAL: J RHEUMATOL 18 (4). 1991. 552-558. 1991
FULL JOURNAL NAME: Journal of Rheumatology
CODEN: JRHUA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The association of thrombosis with antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE) could be due to their interference with natural phospholipid dependent anticoagulant mechanisms. We studied antigenic protein C (APC), functional protein C (FPC), free protein S (FPS), protein S bound to C4 binding protein (C4bp-S), antithrombin III (ATIII), as well as IgG and IgM anticardiolipin antibodies (aCL) in 38 patients with SLE with a history of thromboses and 70 patients with SLE without such history. We found a high frequency of deficiencies of natural anticoagulants in both groups of patients with SLE but, because of patient selection, we could not determine the actual prevalence of these defects. Patients having had a venous thrombosis in the previous year had low C4bp-S more frequently than patients with older or no thromboses. When we divided our patients with SLE into those who had a definite, probable, questionable or no antiphospholipid syndrome (aPS) we found the frequency of C4bp-S deficiency to be significantly higher in those with definite aPS than in those without aPS. Intermediate proportions were found in patients with probable and questionable aPS. The levels of C4bp-S decreased as the levels of aCL, particularly IgG, increased. Stepwise discriminant analysis of natural anticoagulants selected deficiencies of C4bp-S and EFPC with increased ATIII as a set of variables with highest predictive power for classification of patients with and without aPS. Thus, deficiencies of natural anticoagulants may occur frequently in patients with SLE. Those of C4bp-S appear to be related to the presence of aPL associated with evidence of aPS and with thromboses that occurred within a year. A triad of low C4bp-S and FPC and high ATIII may serve to discriminate patients with aPS from those without, suggesting in them the presence of a hypercoagulable state.

1991

19/3,AB/42 (Item 42 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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07571044 BIOSIS NO.: 000091111598
MYXOCOCCUS-XANTHUS PROTEIN C IS A MAJOR SPORE SURFACE PROTEIN
AUTHOR: MCCLEARY W R; ESMON B; ZUSMAN D R
AUTHOR ADDRESS: DEP. MOL. CELL BIOL., UNIV. CALIFORNIA, BERKELEY, CALIF. 94720.
JOURNAL: J BACTERIOL 173 (6). 1991. 2141-2145. 1991
FULL JOURNAL NAME: Journal of Bacteriology
CODEN: JOBAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Fruiting body formation in Myxococcus xanthus involves the aggregation of cells to form mounds and the differentiation of rod-shaped cells into spherical myxospores. The surface of the myxospore is composed of several sodium dodecyl sulfate (SDS)-soluble proteins, the best characterized of which is protein S (Mr, 19,000). We have identified a new major spore surface protein called protein C (Mr, 30,000). Protein C is not present in extracts of vegetative cells but appears in extracts of developing cells by 6 h. Protein C, like protein S, is produced during starvation in liquid medium but is not made during glycerol-induced sporulation. Its synthesis is blocked in certain developmental mutants

but not others. When examined by SDS-polyacrylamide gel electrophoresis, two forms of protein C are observed. Protein C is quantitatively released from spores by %%%treatment%% with 0.1 N NaOH or by boiling in 1% SDS.

It is slowly washed from the spore surface in water but is stabilized by the presence of magnesium. %%%Protein%% %%%C%% %%%binds%% to the surface of spores depleted of protein C and protein S. Protein C is a useful new marker for development in *M. xanthus* because it is developmentally regulated, spore associated, abundant, and easily purified.

%%1991%%

19/3,AB/43 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07433212 BIOSIS NO.: 000091039201
A 58-BASE-PAIR REGION OF THE HUMAN C3 GENE CONFERS
SYNERGISTIC INDUCIBILITY
BY INTERLEUKIN-1 AND INTERLEUKIN-6
AUTHOR: WILSON D R; JUAN T S-C; WILDE M D; FEY G H;
DARLINGTON G J
AUTHOR ADDRESS: DEP. OF PATHOL., BAYLOR COLL. OF MED.,
HOUSTON, TEXAS
77030.
JOURNAL: MOL CELL BIOL 10 (12). 1990. 6181-6191. %%%1990%%
FULL JOURNAL NAME: Molecular and Cellular Biology
CODEN: MCEBD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have cloned the promoter for the human third component of complement (C3) gene and have identified sequences involved in its regulation during the acute-phase response. A construct linking 199 bp of the C3 promoter to the firefly luciferase gene was found to be very responsive to interleukin-1 (IL-1) and modestly responsive to interleukin-6 (IL-6) by transfection analysis in the human hepatoma line Hep3B2. Simultaneous %%%treatment%% with the two cytokines showed a strong synergy between the actions of the two molecules. A 58-bp fragment (-127 to -70 bp) was shown by 5' and 3' deletional mutagenesis to contain cis-acting elements that mediated both the IL-1 response and the IL-1-plus-IL-6 synergistic response of this promoter. When coupled to a heterologous promoter, this fragment enabled the synergistic induction by IL-1 plus IL-6. Sequences homologous to the palindrome ACATTGCACAATCT, which mediates the induction of the IL-6 gene by IL-1 (S. Akira, H. Isshiki, T. Sugita, O. Tanabe, S. Kinoshita, Y. Nishio, T. Nakajima, T. Hirano, and T. Kishimoto, EMBO J. 9:1987-1996, 1990), and the core sequence of the IL-6-responsive element of the rat α_2 -macroglobulin gene (CTGGGA; M. Hattori, L. J. Abraham, W. Northemann, and G. H. Fey, Proc. Natl. Acad. Sci. USA 87:2364-2368, 1990) are contained within this fragment in immediate juxtaposition and partially overlapping. Site-directed mutagenesis within this homology region drastically reduced the inducibility of the C3 promoter by either cytokine. DNase I footprinting analysis defined a binding site for the transcription factor CCAAT/enhancer-%%binding%% %%%protein%% (%%%C%%/EBP), which included the IL-1-responsive element-like sequence. No differences were seen between the footprints generated by using extracts from unstimulated and IL-1-stimulated Hep3B2 cells. However, gel retardation analysis revealed two IL-1-specific bands. The data suggest that the induction by IL-1 is mediated by a factor belonging to the family of C/EBP-related proteins.

%%1990%%

19/3,AB/44 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07420800 BIOSIS NO.: 000091026789
IL-6DBP A NUCLEAR PROTEIN INVOLVED IN INTERLEUKIN-6
SIGNAL TRANSDUCTION

DEFINES A NEW FAMILY OF LEUCINE ZIPPER PROTEINS
RELATED TO C-EBP
AUTHOR: POLI V; MANCINI F P; CORTESE R
AUTHOR ADDRESS: DEP. GENETICS DEV., COLL. PHYSICIANS
SURGEONS, COLUMBIA
UNIV., NEW YORK, N.Y. 10032.
JOURNAL: CELL 63 (3). 1990. 643-653. %%%1990%%
FULL JOURNAL NAME: Cell
CODEN: CELLB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We analyzed a family of proteins from hepatoma cell nuclei that bind to interleukin-6 responsive elements (IL-6REs) of several acute-phase genes. This family is characterized by leucine zipper domains compatible with that of the CCAAT/enhancer %%%binding%% %%%protein%% (%%%C%%/EBP). A cDNA clone coding for a member of the family, IL-6DBP, was isolated; it is strongly homologous to C/EBP in the region of the basic domain and in the leucine zipper sequence. IL-6DBP and C/EBP can interact in vitro to form heterodimers that bind to DNA with the same specificity as the respective homodimers, and they can interact functionally in vivo. Both the DNA binding activity and the trans-activating capacity of IL-6DBP are induced in hepatoma cells by %%%treatment%% with IL-6 through a posttranslational mechanism, implicating it as a nuclear target of IL-6 and as a mediator of the IL-6-dependent transcriptional activation of liver genes during the acute-phase response.

%%1990%%

19/3,AB/45 (Item 45 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07255794 BIOSIS NO.: 000090035670
INHIBITION OF COFACTOR ACTIVITY OF PROTEIN S BY A
COMPLEX OF PROTEIN S AND
C4B-BINDING PROTEIN EVIDENCE FOR INACTIVE TERNARY
COMPLEX FORMATION
BETWEEN PROTEIN S C4B-BINDING PROTEIN AND ACTIVATED
PROTEIN C
AUTHOR: NISHIOKA J; SUZUKI K
AUTHOR ADDRESS: DIV. ENZYME CYTOL., INST. ENZYME RES.,
UNIVERSITY
TOKUSHIMA, KURAMOTO-CHO 3, TOKUSHIMA 770, JPN.
JOURNAL: J BIOL CHEM 265 (16). 1990. 9072-9076. %%%1990%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: To elucidate the mechanism by which C4b-binding protein inhibits the cofactor activity of protein S for anticoagulant-activated protein C, the interactions between protein S, activated %%%protein%% %%%C%%, and C4b-%%binding%% protein were studied using solid-phase enzyme immunoassays. Both activated %%%protein%% %%%C%% and C4b-%%binding%% protein bound to protein S fixed to microplate wells. C4b-binding protein did not inhibit the %%%binding%% of activated %%%protein%% to protein S, nor did activated %%%protein%% %%%C%% inhibit the %%%binding%% of C4b-binding protein to protein S. Activated %%%protein%% %%%C%% bound to a protein S-C4b-binding protein complex which was cross-linked with a chemical reagent as well as it bound to free protein S. Protein S-C4b-binding protein complex competitively inhibited activated %%%protein%% to free protein S and also the cofactor activity of free protein S. Immunoblotting analysis showed ternary complex formation which protein S, C4b-binding protein, and activated protein C in the liquid phase by

%%treatment%% with the cross-linking reagent. These finding suggest that the protein S-C4b-binding protein complex inhibits the cofactor activity of free protein S probably by inhibition of functionally active protein S-activated protein Complex formation by the apparent competitive formation of an inactive ternary complex with protein S, C4b-binding protein, and activated protein C.

%%1990%%

19/3,AB/46 (Item 46 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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06660930 BIOSIS NO.: 000087103107
AVIAN RETROVIRAL LONG TERMINAL REPEATS BIND
CCAAT-ENHANCER-BINDING PROTEIN
AUTHOR: RYDEN T A; BEEMON K
AUTHOR ADDRESS: DEP. BIOL., JOHNS HOPKINS UNIV.,
BALTIMORE, MD. 21218.
JOURNAL: MOL CELL BIOL 9 (3). 1989. 1155-1164. %%1989%%
FULL JOURNAL NAME: Molecular and Cellular Biology
CODEN: MCEBD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: DNA-protein interactions involving enhancer and promoter sequences within the U3 regions of several avian retroviral long terminal repeats (LTRs) were studied by DNase I footprinting. The rat CCAAT/enhancer-%%binding%% protein%%, %%C%%/EBP, %%bound%% to all four viral LTRs examined. The Rous sarcoma virus binding site corresponded closely to the 5' limit of the LTR enhancer; nucleotides -225 to -188 were protected as a pair of adjacent binding domains. The Fujinami sarcoma virus LTR bound C/EBP at a single site at nucleotides -213 to -195. C/EBP also bound to the promoter region of the enhancerless Rous-associated virus-0 LTR at nucleotides -77 to -57. The avian myeloblastosis virus LTR bound C/EBP at three sites; nucleotides -262 to -246, -154 to -134, and -55 to -39. We have previously observed binding of C/EBP to an enhancer in the gag gene of avian retroviruses. A heat-%%treated%% nuclear extract from chicken liver bound to all of the same retroviral sequences as did C/EBP. Alignment of the avian retroviral binding sequences with the published binding sites for C/EBP in two CCAAT boxes and in the simian virus 40, polyoma, and murine sarcoma virus enhancers suggested TGTNNGTCAAGT as a consensus sequence for binding of C/EBP. When two bases of this consensus sequence were altered by site-specific mutagenesis of the Rous sarcoma virus LTR, binding of the heat-stable chicken protein was eliminated.

%%1989%%

19/3,AB/47 (Item 47 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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06177645 BIOSIS NO.: 000086011827
A CONSERVED EPIOTOPE ON SEVERAL HUMAN VITAMIN
K-DEPENDENT PROTEINS LOCATION
OF THE ANTIGENIC SITE AND INFLUENCE OF METAL IONS ON
ANTIBODY BINDING
AUTHOR: CHURCH W R; MESSIER T; HOWARD P R; AMIRAL J;
MEYER D; MANN K G
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. VT., HEALTH SCI.
COMPLEX, GIVEN
BUILD., BURLINGTON, VT. 05405.
JOURNAL: J BIOL CHEM 263 (13). 1988. 6259-6267. %%1988%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A murine monoclonal antibody (designated H-11) produced by injecting mice with purified human protein C was found to bind several human vitamin K-dependent proteins. Using a solid-phase competitive

radioimmunoassay with antibody immobilized onto microtiter plates, binding of 125I-labeled protein C to the antibody was inhibited by increasing amounts of protein C, prothrombin, and Factors X and VII over a concentration range of 1 .times. 10-8 to 1 .times. 10-6 M. Other vitamin K-dependent proteins including Factor IX and protein S did not inhibit or inhibited only at the highest concentration %%binding%% of radiolabeled %%protein%% %%C%% to the immobilized antibody.

Chemical

%%treatment%% of prothrombin with a variety of agents including denaturation by sodium dodecyl sulfate, reduction with mercaptoethanol followed by carboxymethylation with iodoacetic acid, citraconylation of lysine residues, removal of metal ion with EDTA, or heat decarboxylation did not destroy the antigenic site recognized by the antibody as measured by immunoblotting of prothrombin or prothrombin derivative immobilized onto nitrocellulose. Immunoblotting of purified vitamin K-dependent polypeptides with the monoclonal antibody following sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electrophoretic transfer to nitrocellulose indicated that the antigenic site was found on the light chains of protein C and Factor X. Chymotrypsin digestion of prothrombin and isolation on QAE-Sephadex of the peptide representing amino-terminal residues 1-44 of prothrombin further localized the antigenic site recognized by the monoclonal antibody to the highly conserved .gamma.-carboxyglutamic acid-containing domain. The exact location of the antigenic determinant for antibody H-11 was established using synthetic peptides. Antibody H-11 bound specifically to synthetic peptides corresponding to residues 1-12 of Factor VII and 1-22 of protein C. Comparison of protein sequences of bovine and human vitamin K-dependent proteins suggests that the sequence Phe-Leu-Glu-Glu-Xaa-Arg/Lys is required for antibody binding. The glutamic acid residues in this peptide segment are the first 2 .gamma.-carboxyglutamic acid residues near the amino-terminal end in the native proteins. Increasing concentrations of Ca2+, Mg2+, or Mn2+ partially inhibited %%binding%% of 125I-%%protein%% %%C%% to the antibody in a solid-phase assay system with half-maximal binding observed at divalent metal ion concentrations of 2, 4, and 0.6 mM, respectively. The antigenic site thus recognized by monoclonal antibody H-11 is located at the amino-terminal region in the highly conserved .gamma.-carboxyglutamic acid-containing domains of several, but not all, vitamin K-dependent proteins. Furthermore, the binding of metal ions to the protein causes loss of the determinant recognized by the antibody due possibly to a metal ion-dependent conformational change of the amino acid residues located at the amino terminus.

%%1988%%

19/3,AB/48 (Item 48 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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05756719 BIOSIS NO.: 000084105126
THROMBOMODULIN A COFACTOR OF PROTEIN C ACTIVATION
ISOLATION
CHARACTERIZATION AND APPLICATION FOR LABORATORY
MEDICINE
AUTHOR: KUSUMOTO H
AUTHOR ADDRESS: DEP. LAB. MED., MIE UNIV. SCH. MED., TSU,
MIE 514, JPN.
JOURNAL: MIE MED J 37 (1). 1987. 145-172. %%1987%%
FULL JOURNAL NAME: Mie Medical Journal
CODEN: MMJJA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The present study was undertaken to isolate and characterize thrombomodulin, a cofactor in thrombin-catalyzed activation of protein C, from bovine and human lungs. Thrombomodulin was also applied to a functional assay for protein C in plasma. Thrombomodulin isolated by diisopropylphosphate-thrombin-agarose column chromatography was a single polypeptide chain with apparent molecular weights of 78,000 and 105,000 before and after reduction, respectively, on sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. The overall amino acid compositions of bovine and human thrombomodulin were similar to that of the rabbit protein which had been isolated previously (13). The NH2-terminal sequence of human thrombomodulin had a high homology of 64%

with the bovine protein. Thrombomodulin from both species was unusually stable in 1% SDS and 8 M urea, at pH's 2 and 10, and with heat treatment at 60 degree C, but was unstable against 2-mercaptoethanol treatment. Expression of thrombomodulin cofactor activity was Ca2+-dependent. Formation of an equimolar complex of thrombin and thrombomodulin was required for maximal protein C activation. Bovine thrombomodulin strongly blocked thrombin-induced fibrinogen clotting and platelet activation as did the rabbit protein, but the inhibitory activity of the human protein was very weak. Thrombomodulin had no influence on the inhibition of thrombin by antithrombin III with or without heparin, protein C inhibitor or synthetic thrombin inhibitors. The functional assay for plasma protein C using thrombomodulin was developed to enable detection of dysfunctional protein C molecules. The assay consisted of three steps; (a) extraction of protein C from plasma by barium citrate precipitation, followed by monoclonal anti-protein C antibody adsorption; (b) activation of protein C to protein C% to the antibody by thrombin-thrombomodulin; (c) measurement of activated protein C using a synthetic chromogenic substrate, S-2366. This assay proved effective in distinguishing normal from abnormal protein C.

19/3,AB/49 (Item 49 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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05238970 BIOSIS NO.: 000082079592
THE BINDING OF ACTIVATED PROTEIN C TO FACTORS V AND VA
AUTHOR: KRISHNASWAMY S; WILLIAMS E B; MANN K G
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. VERMONT, BURLINGTON, VERMONT 05405.
JOURNAL: J BIOL CHEM 261 (21). 1986. 9684-9693.
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Activated protein C has been derivatized with the active site-directed fluorophore 2-(dimethylamino)-6-naphthalenesulfonylglutamylglycylarginyl chloromethyl ketone (2,6-DEGR-APC). Covalently modified activated protein has been used to investigate the binding interactions of the protein to factors V and Va in the presence of phospholipid vesicles. The fluorescence polarization of the 6-dimethylaminonaphthalene-2-sulfonyl moiety increased saturably with increasing phospholipid concentrations in the presence or absence of factor V or Va. Differences in the limiting polarization values indicated distinguishable differences in the interactions between 2,6-DEGR-APC and phospholipid in the presence of factor V or Va. The dissociation constant calculated for the 2,6-DEGR-APC/phospholipid interaction (7.3 times 10-8 M) was not significantly altered by factor V but was decreased to 7 times 10-9 M in the presence of factor Va. The interaction between 2,6-DEGR-APC and factor V or Va was characterized by a 1:1 stoichiometry. The binding of 2,6-DEGR-APC to factor V or Va in the presence of phospholipid could be reduced in a competitive manner by diisopropylphosphofluoridate-treated activated protein C. An analysis of the displacement curves indicated that the binding of 2,6-DEGR-APC was indistinguishable from the binding of diisopropylphosphofluoridate-treated activated protein C. The interaction between 2,6-DEGR-APC and phospholipid-bound factor Va was further examined using the isolated subunits of factor Va. Fluorescence polarization changes observed with component E of Va (light chain) closely corresponded with the changes observed with factor Va, whereas isolated component D (heavy chain) had little influence on the binding of 2,6-DEGR-APC to phospholipid vesicles. The data presented are consistent with the interpretation that component E of factor Va contains a binding site for activated protein C.

1986

19/3,AB/50 (Item 50 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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05179729 BIOSIS NO.: 000082020350
SIMPLE IMMUNOCHROMOMETRIC ASSAY FOR PROTEIN C ACTIVITY
AUTHOR: EXNER T; KOUTTS J
AUTHOR ADDRESS: HAEMATOL. DEP., WESTMEAD HOSP., WESTMEAD, SYDNEY, AUST. 2145.
JOURNAL: J LAB CLIN MED 107 (5). 1986. 405-411.
FULL JOURNAL NAME: Journal of Laboratory and Clinical Medicine
CODEN: JLCMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Protein C binds readily from human plasma to antibody-coated wells, where it may be quantitated with an iodine 125-labeled antibody to protein C. Treatment with thrombin results in a small reduction in the protein C antigen detectable by this immunoradiometric assay (IRMA). However, activated protein C resulting from thrombin treatment and retained by the antibody on a solid phase may be detected by an overnight incubation with chromogenic substrates S-2366 or CBS 34.47. The immunochromometric assay (ICMA, analogous to IRMA) described uses of heterologous antibody to protein C, activation with relatively low concentrations of bovine thrombin, and quantitation by hydrolysis of chromogenic substrate in a convenient 96-well microtiter plate system. The correlation between IRMA and ICMA protein C results was found to be good with normal persons and patients with liver disease. Patients taking oral anticoagulants had reduced protein C antigen (IRMA) but even lower protein C by ICMA, indicating that inactive forms were present.

1986

19/3,AB/51 (Item 51 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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04761732 BIOSIS NO.: 000080064859
DETERMINATION OF PLASMA PROTEIN S THE PROTEIN COFACTOR OF ACTIVATED PROTEIN C
AUTHOR: BERTINA R M; VAN WIJNGAARDEN A; REINALDA-POOT J; POORT S R; BOM V J
AUTHOR ADDRESS: HAEMOSTASIS THROMBOSIS RES. UNIT, DEP. HAEMATOL., LEIDEN UNIV. HOSP., RIJNSBURGERWEG 10, 2333 AA LEIDEN, NETHERLANDS.
JOURNAL: THROMB HAEMOSTASIS 53 (2). 1985. 268-272.
FULL JOURNAL NAME: Thrombosis and Haemostasis
CODEN: THHAD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Protein S, an important cofactor of activated protein C, and C4b-binding protein were purified from human plasma. Specific antibodies against the purified proteins were raised in rabbits and used for the development of immunologic assays for these proteins in plasma: an immunoradiometric assay for protein S (which measures both free protein S and protein S complexed with C4b-binding protein) and an electroimmunoassay for C4b-binding protein. Ranges for the concentrations of these proteins were established in healthy volunteers and patients using oral anticoagulant therapy. A slight decrease in protein S antigen was observed in patients with liver disease (0.78 +/- 0.25 U/ml); no significant decrease in protein S was observed in patients with DIC [disseminated intravascular coagulation] (0.95 +/- 0.25 U/ml). Criteria were developed for the laboratory diagnosis of an isolated protein S deficiency.

1985

19/3,AB/52 (Item 52 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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04651784 BIOSIS NO.: 000079064821
QUANTITATION OF HUMAN PROTEIN S IN THE PLASMA OF
NORMAL AND WARFARIN-
TREATED INDIVIDUALS BY RADIOIMMUNOASSAY
AUTHOR: FAIR D S; REVAK D J
AUTHOR ADDRESS: DEP. IMMUNOL., RES. INST. SCRIPPS CLINIC,
10666 N. TORREY
PINES ROAD, LA JOLLA, CALIF., USA.
JOURNAL: THROMB RES 36 (6). 1984 (RECD. 1985). 527-536.
1984
FULL JOURNAL NAME: Thrombosis Research
CODEN: THBRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Protein S was purified from human plasma and used to raise
monospecific antibodies. A double antibody equilibrium radioimmunoassay
was constructed and met all the requirements for a sensitive, accurate
and specific determination of protein S. The sensitivity of the assay was
between 8 and 250 ng of protein S/ml and the coefficient of variation was
2-6% within assays and 13-19% between assays. Complement C4b-
binding protein or protein C did not
effect the
measurement of protein S. Complete competition with parallel slopes of
inhibition was seen among purified protein S and plasma from normal and
warfarin-treated individuals indicating immunochemical identity
and
validating the measurement of protein S in plasma. The concentration of
protein S in normal plasma (n = 24) was 23.4 +/- 4.42 .mu.g/ml and in
plasma from warfarin-treated individuals (n = 24) was 12.6 +/-
3.92 .mu.g/ml. A common feature of individuals undergoing warfarin
therapy is the reduction of approx. 50% in the concentration of each of
the vitamin K-dependent proteins.

1984

19/3,AB/53 (Item 53 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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04209345 BIOSIS NO.: 000077035389
CIRCULATING IMMUNE COMPLEXES AND COMPLEMENT C-1
ACTIVATION IN PATIENTS WITH
RAPIDLY PROGRESSIVE GLOMERULO NEPHRITIS BEFORE AND
AFTER TREATMENT
WITH IMMUNO SUPPRESSION AND PLASMA EXCHANGE
AUTHOR: SJOHOLM A G; BRUN C; LARSEN S; THYSELL H
AUTHOR ADDRESS: DEP. NEPHROL., UNIV. HOSP., S-221 85 LUND.
JOURNAL: INT ARCH ALLERGY APPL IMMUNOL 72 (1). 1983. 9-15.
1983
FULL JOURNAL NAME: International Archives of Allergy and Applied
Immunology
CODEN: IAAAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Well-known assays (C1q binding assay, C1q deviation test,
solid-phase C1q binding assay, solid-phase conglutinin binding assay, and
the platelet aggregation test) for detection of circulating immune
complexes (CIC) were used in 30 patients with different kinds of rapidly
progressive glomerulonephritis. In 89% of the patients evidence of CIC
was found in at least one of the assays; 81% of the patients were
positive in the C1q binding assay and/or the conglutinin binding assay
with addition of complement. CIC were more often detected by several
assays, and with higher values in patients with systemic disease than in
patients with renal involvement alone. CIC were found in 2 patients with
Goodpasture's syndrome. Fifteen patients were reexamined after
treatment with plasma exchange, when the disease was
clinically
inactive. The patients were still on immunosuppressive
treatment.
In most of these, CIC were detectable, but with lower values than at the

start of treatment. Before treatment, high levels of
C.hivin.1r-C.hivin.1s-C.hivin.1 inactivator complexes suggested increased
C1 activation in 93% of the patients. C-reactive protein was raised, and
the concentrations of C1q, C1s, C4, C3 and factor B were normal or high
in most of the patients. Pronounced hypocomplementemia was found only in
2 patients with systemic lupus erythematosus (SLE). After
treatment
, the levels of C-reactive protein, C1q, C1s, C3 and factor B had
decreased in the non-SLE patients, while the average levels of C4 and
C.hivin.1r-C.hivin.1s-C.hivin.1 inactivator complexes were essentially
unchanged.

1983

19/3,AB/54 (Item 54 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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02947407 BIOSIS NO.: 000069055525
THE INHIBITION OF BLOOD COAGULATION BY ACTIVATED
PROTEIN C THROUGH THE
SELECTIVE INACTIVATION OF ACTIVATED FACTOR-V
AUTHOR: WALKER F J; SEXTON P W; ESMON C T
AUTHOR ADDRESS: SECT. EXP. PATHOL. MED., UNIV. OKLA.
HEALTH SCI. CENT.,
OKLAHOMA CITY, OKLA. 73190, USA.
JOURNAL: BIOCHIM BIOPHYS ACTA 571 (2). 1979 (RECD. 1980).
333-342.
1979
FULL JOURNAL NAME: Biochimica et Biophysica Acta
CODEN: BBACA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Activated protein C inhibited factor [F] Xa initiated clotting of
[bovine] plasma. Activated protein C did not inhibit prothrombin
activation by FXa and Ca2+ or FXa, Ca2+ and lipid. Activated protein C
did inhibited prothrombin activation by FXa, Ca2+ and FVa or FXa, Ca2+,
lipid and FVa. Excess FVa could reverse the inhibition of prothrombin
activation. Incubation of FV with activated protein C had little effect
of FV activity in the presence or absence of phospholipid. Preincubation
of FV with activated protein C had no effect upon the degree to which FV
could be activated. When FV was activated with thrombin in the presence
of activated protein C, rapid decline in FVa activity was observed. When
activated protein C was incubated with purified FVa in the absence of
thrombin, a similar rapid decay in FVa activity was observed. Activated
protein C-catalyzed decay of FVa activity was not obligatorily dependent
on the presence of lipid. Lipid enhanced the rate of inactivation.
Analysis of sodium dodecyl sulfate gels of FV or Va treated
with
activated protein C indicated that activated protein C degraded a slow
migrating band of the FV doublet and that it also was able to degrade
both the heavy and light chains of FVa. Activated Protein C could
apparently inhibit FXa initiated clotting by degrading FVa. FVa could be
protected from activated protein C inactivation by the presence of FXa,
suggesting that activated protein C binds to FVa at or
near the FXa binding site. Specificity of activated protein C for FVa and
ability of FXa to stabilize FVa may play important functions in the
regulation of blood coagulation.

1979

19/3,AB/55 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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07034725 EMBASE No: 1997315138
Signaling pathways through which insulin regulates CCAAT/enhancer
binding protein (C/EBPalpha)
phosphorylation and gene
expression in 3T3-L1 adipocytes. Correlation with GLUT4 gene expression
Hemati N.; Ross S.E.; Erickson R.L.; Groblewski G.E.; MacDougald O.A.
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Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1997
 272/41 (25913-25919)
 CODEN: JBCHA ISSN: 0021-9258
 DOCUMENT TYPE: Journal; Article
 LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
 NUMBER OF REFERENCES: 51

%%Treatment%% of 3T3-L1 adipocytes with insulin (IC50 ~200 pM insulin) or insulin-like growth factor-I (IC50 ~200 pM IGF-I) stimulates dephosphorylation of CCAAT/enhancer binding protein alpha (C/EBPalpha), a transcription factor involved in preadipocyte differentiation. As assessed by immunoblot analysis of one- and two-dimensional PAGE, insulin appears to dephosphorylate one site within p30C/EBPalpha and an additional site within p42C/EBPalpha. Consistent with insulin causing dephosphorylation of C/EBPalpha through activation of phosphatidylinositol 3-kinase, addition of phosphatidylinositol 3-kinase inhibitors (e.g. wortmannin) blocks insulin-stimulated dephosphorylation of C/EBPalpha. In the absence of insulin, wortmannin or LY294002 enhance C/EBPalpha phosphorylation. Similarly, blocking the activity of FKBP-rapamycin-associated protein with rapamycin increases phosphorylation of C/EBPalpha in the absence of insulin. Dephosphorylation of C/EBPalpha by insulin is partially blocked by rapamycin, consistent with a model in which activation of FKBP-rapamycin-associated protein by phosphatidylinositol 3-kinase results in dephosphorylation of C/EBPalpha. The dephosphorylation of C/EBPalpha by insulin, in conjunction with the insulin-dependent decline in C/EBPalpha mRNA and protein, has been hypothesized to play a role in repression of GLUT4 transcription by insulin. Consistent with this hypothesis, the decline of GLUT4 mRNA following exposure of adipocytes to insulin correlates with dephosphorylation of C/EBPalpha. However, the repression of C/EBPalpha mRNA and protein levels by insulin is blocked with an inhibitor of the mitogen-activated protein kinase pathway without blocking the repression of GLUT4 mRNA, thus dissociating the regulation of C/EBPalpha and GLUT4 mRNAs by insulin. A decline in C/EBPalpha mRNA and protein may not be required to suppress GLUT4 transcription because insulin also induces expression of the dominant-negative form of C/EBPbeta (liver inhibitory protein), which blocks transactivation by C/EBP transcription factors.

19/3,AB/56 (Item 2 from file: 73)
 DIALOG(R)File 73:EMBASE
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06987235 EMBASE No: 1997273316
 Serum mannan-binding lectin (MBL) in patients with infection: Clinical and laboratory correlates
 Aittoniemi J.; Rintala E.; Miettinen A.; Soppi E.
 J. Aittoniemi, Department of Clinical Microbiology, Tampere University Hospital, P.O. Box 2000, FIN-33521 Tampere Finland
 APMIS (APMIS) (Denmark) 1997, 105/8 (617-622)
 CODEN: APMSE ISSN: 0903-4641
 DOCUMENT TYPE: Journal; Article
 LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
 NUMBER OF REFERENCES: 17

In this study, we determined the serum levels of mannan-binding lectin (MBL) in patients with suspected or documented infection to characterize the possible role of MBL in the susceptibility to infection. We also investigated the kinetics of MBL during the infection and correlated the concentrations of MBL with those of acute-phase reactants C-reactive protein (CRP) and group II phospholipase A2 (PLA2-II) and cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha). The frequency of MBL deficiency in the patients with signs of infection did not differ from that of controls. In four patients with MBL deficiency, the infections were caused by common pathogens and the outcome was normal. The mean MBL concentration in the patients with signs of infection was significantly higher than in the healthy controls (9.88 and 4.48 mg/l, respectively; p<0.05). The highest mean MBL concentration was observed in patients with clinically or microbiologically documented bacterial infection. During follow-up, the MBL concentration altered

individually in different patients, but no particular change in pattern in the MBL concentration could be demonstrated in any patient group. Of the acute-phase reactants in the circulation, only CRP and IL-1 showed a weak, albeit significant, negative correlation with the concentration of MBL. In conclusion, the deficiency of MBL was not shown to be an independent risk factor for infection in the adult population studied. The concentration of MBL did not follow the change in pattern of other acute-phase reactants and cytokines during the acute phase response. Therefore, measurement of the MBL concentration as an acute-phase reactant is not useful in the diagnosis or follow-up of infection. On the other hand, the deficiency of MBL can be detected reliably by serological methods even during an infection.

19/3,AB/57 (Item 3 from file: 73)
 DIALOG(R)File 73:EMBASE
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06689867 EMBASE No: 1996354799
 Calciphylaxis (I)
 Walsh J.S.; Fairley J.A.; Hafner J.
 Department of Dermatology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226 United States
 Journal of the American Academy of Dermatology (J. AM. ACAD. DERMATOL.) (United States) 1996, 35/5 (786-787)
 CODEN: JAADD ISSN: 0190-9622
 DOCUMENT TYPE: Journal; Letter
 LANGUAGE: ENGLISH

19/3,AB/58 (Item 4 from file: 73)
 DIALOG(R)File 73:EMBASE
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06612031 EMBASE No: 1996276804
 cAMP activation of phosphoenolpyruvate carboxykinase transcription in renal LLC-PK1-Fsp + cells
 Liu X.; Curthoys N.P.
 Dept. of Biochemistry/Molec. Biology, Colorado State University, Fort Collins, CO 80523-1870 United States
 American Journal of Physiology - Renal Fluid and Electrolyte Physiology (AM. J. PHYSIOL. RENAL FLUID ELECTROLYTE PHYSIOL.) (United States) 1996, 271/2 40-2 (F347-F355)
 CODEN: AJPFD ISSN: 0363-6127
 DOCUMENT TYPE: Journal; Article
 LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Phosphoenolpyruvate carboxykinase (PCK) is a key regulatory enzyme in renal ammoniogenesis and gluconeogenesis. LLC-PK1-Fsp + cells are porcine renal proximal tubule-like cells that express significant levels of the cytosolic PCK. %%Treatment%% of subconfluent LLC-PK1-Fsp + cells with 0.1 mM 8-(4-chlorophenylthio)-adenosine 3',5'-cyclic monophosphate (CPT-cAMP) for 8 h causes a 21-fold increase in PCK mRNA. This response is very rapid and is not inhibited by 0.5 mM cycloheximide, indicating that ongoing protein synthesis is not required. Similarly, cells transfected with PCK inf 4inf 9inf 0CAT exhibit an 8- to 10-fold increase in chloramphenicol acetyltransferase (CAT) activity when %%treated%% with cAMP for 24 h. The addition of okadaic acid, a protein phosphatase inhibitor, both stimulated the CAT activity and potentiated the cAMP effect by twofold, suggesting that phosphorylation may contribute to the transcriptional activation. Assays using a series of PCK-CAT constructs containing specific deletions or block mutations established that the CRE-1 the P3(II) elements are required for the cAMP response. Cotransfection experiments using dominant negative expression vectors indicated that a CCAAT enhancer %%binding%% protein (%%C%%/EBP) transcription factor, and not CREB, mediates cAMP activation of transcription in LLC-PK1-Fsp + cells.

19/3,AB/59 (Item 5 from file: 73)
 DIALOG(R)File 73:EMBASE

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06560091 EMBASE No: 1996221019

GADD153/CHOP, a DNA damage-inducible protein, reduced CAAT/enhancer binding protein activities and increased apoptosis in 32d cl3 myeloid cells
Friedman A.D.
Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21287
United States
Cancer Research (CANCER RES.) (United States) 1996, 56/14 (3250-3256)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

GADD153/CHOP is a DNA damage-inducible, nuclear leucine zipper protein that is capable of producing a G1/S arrest in fibroblastic cells and of dimerizing with and inhibiting CAAT/enhancer binding protein (C/EBP) activities. CHOP was induced in 32D cl3 myeloid cells exposed to methylmethane sulfonate (MMS), a DNA alkylating agent. The degree of induction was dependent upon the dose of MMS to which the cells were exposed. CHOP was not expressed, at least at similar levels, during 32D cl3 cell granulocytic differentiation or during their apoptosis upon growth factor withdrawal. High-level expression of exogenous CHOP in 32D cl3 cells markedly inhibited the trans-activation activities of endogenous C/EBPs. These cells proliferated in IL-3, although low-level ongoing apoptosis not observed with control cells was detected. When these cultures were transferred to granulocyte colony-stimulating factor (G-CSF), the majority of the cells underwent apoptosis, although the levels of CHOP did not increase. Similarly, 32D cl3 cells treated with doses of MMS sufficient to induce endogenous CHOP underwent apoptosis more rapidly when placed in G-CSF-containing, compared with interleukin 3 (IL-3)-containing, medium. However, induction of CHOP by MMS was similar in IL-3 and in G-CSF. The heightened sensitivity of 32D cl3 cells to CHOP in G-CSF could result either from the loss of IL-3-specific signals or from increased expression of C/EBPs. Because myeloid leukemias express C/EBPalpha, induction of CHOP might contribute to their chemotherapy-induced apoptosis, and alterations in CHOP expression could contribute to their development of chemotherapy resistance.

19/3,AB/60 (Item 6 from file: 73)

DIALOG(R)File 73:EMBASE

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06455576 EMBASE No: 1996118153

CCAAT/enhancer-binding protein (C/EBP) inhibits cell proliferation through the p21 (WAF-1/CIP-1/SDI-1) protein
Timchenko N.A.; Wilde M.; Nakanishi M.; Smith J.R.; Darlington G.J.
Department of Pathology, Baylor College of Medicine, Houston, TX 77071
United States
Genes and Development (GENES DEV.) (United States) 1996, 10/7 (804-815)
CODEN: GEDEE ISSN: 0890-9369
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

C/EBPalpha has a role in growth arrest and differentiation of mouse preadipocytes. To study the mechanism of C/EBPalpha-induced growth arrest, we developed a cell line, HT1, that contained the human C/EBPalpha gene under Lac repressor control. IPTG-induced C/EBPalpha caused inhibition of cell proliferation and DNA synthesis as measured by colony growth assays, cell counting, and BrdU uptake. A number of proteins that are known to be involved in the regulation of the cell cycle, such as cyclin-dependent kinase (CDK) 2 and CDK4, proliferating cell nuclear antigen (PCNA), p53, c-fos, and the CDK inhibitor p16 and p27 were investigated by Western analysis. No change in their expression was observed. However, the p21 (WAF-1/CIP-1/SDI-1) protein was significantly elevated in growth-arrested

HT1 cells. Elevation of p21/SDI-1 mRNA (threefold) and activation of the p21/SDI-1 promoter by C/EBPalpha did not account for the 12- to 20-fold increase in p21/SDI-1 protein. Protein synthesis inhibition by cycloheximide (CHX) indicated that the half-life of p21/SDI-1 in dividing HT1 cells was ~30 min. However, in C/EBPalpha growth-arrested cells, the level of the p21/SDI-1 did not change for >80 min after CHX addition. Our studies demonstrate that C/EBPalpha activates p21/SDI-1 by increasing p21/SDI-1 gene expression and by post-translational stabilization of p21/SDI-1 protein. Furthermore, induction of p21/SDI-1 is responsible for the ability of C/EBPalpha to inhibit proliferation because transcription of antisense p21/SDI-1 mRNA eliminated growth inhibition by C/EBPalpha.

19/3,AB/61 (Item 7 from file: 73)

DIALOG(R)File 73:EMBASE

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06338984 EMBASE No: 1995369032

Effect of phenylephrine and prazosin on the somatostatinergic system in the rat frontoparietal cortex
Lopez-Sanudo S.; Rodriguez-Martin E.; Martin-Espinosa A.; Arilla E.
Unidad de Neuroendocrin. Molecular, Departamento de Bioquímica, Facultad de Medicina, E-28871, Alcala de Henares, Madrid Spain
Peptides (PEPTIDES) (United States) 1995, 16/8 (1453-1459)
CODEN: PEPTD ISSN: 0196-9781
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Somatostatin (SS) and noradrenaline (NA) are distributed in the rat cerebral cortex, and seizure activity is one of the aspects of behavior affected by both neurotransmitters. Due to the possible interaction between both neurotransmitter systems, we studied whether phenylephrine, an alpha1-adrenoceptor agonist, and prazosin, an alpha1-adrenoceptor antagonist, can modulate SS-like immunoreactivity (SS-LI) levels, binding of (sup 125I)SS to its specific receptors, the ability of SS to inhibit adenylate cyclase (AC) activity, and the guanine nucleotide binding regulatory protein (G-protein) and cAMP in the Sprague-Dawley rat frontoparietal cortex. An IP dose of 2 or 4 mg/kg of phenylephrine injected 7 h before decapitation decreased the number of SS receptors and increased the apparent affinity in frontoparietal cortex membranes. An IP dose of 20 or 25 mg/kg of prazosin administered 8 h before decapitation increased the number of SS receptors and decreased their apparent affinity. The administration of prazosin before the phenylephrine injection prevented the phenylephrine-induced changes in SS binding. The addition of phenylephrine and/or prazosin 10 sup -sup 5 M to the incubation medium changed neither the number nor the affinity of the SS receptors in the frontoparietal cortex membranes. Phenylephrine or prazosin affected neither SS-LI content nor the basal or forskolin (FK)-stimulated AC activities in the frontoparietal cortex. In addition, SS caused an equal inhibition of AC activity in frontoparietal cortex membranes of phenylephrine- and prazosin-treated rats compared with the respective control group. Finally, phenylephrine and prazosin did not vary the pertussis toxin (PTX)-catalyzed ADP ribosylation of G(i)- and/or G(o)-proteins. These results suggest that the above-mentioned changes are related to the phenylephrine activation of alpha1-adrenoceptors or to the blocking of these receptors by prazosin. In addition, these data provide further support for a functional interrelationship between the alpha1-adrenergic and somatostatinergic systems in the rat frontoparietal cortex.

19/3,AB/62 (Item 8 from file: 73)

DIALOG(R)File 73:EMBASE

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06300656 EMBASE No: 1995330542

Transcriptional regulation of human prostaglandin-endoperoxide synthase-2 gene by lipopolysaccharide and phorbol ester in vascular endothelial cells. Involvement of both nuclear factor for interleukin-6 expression site and cAMP response element
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Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1995
270/42 (24965-24971)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

There exist two distinct isozymes of prostaglandin-endoperoxide synthase (PES). PES-2 mRNA is synergistically induced by lipopolysaccharide (LPS) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in bovine arterial endothelial cells. On the other hand, PES-1 mRNA is constitutively expressed under these conditions. Therefore, the promoter activities of the human genes for PES-1 and -2 in bovine arterial endothelial cells were examined. The 5'-flanking region of the human PES-2 gene (nucleotides -327 to +59) showed promoter activity inducible by LPS and TPA using transient transfection analysis, whereas that of the PES-1 gene (nucleotides -1010 to +69) showed constitutive promoter activity. Destruction of both consensus sequences for the nuclear factor responsible for the interleukin-6 expression (NF-IL6) site (nucleotides -132 to -124) and the cyclic AMP response element (CRE) (nucleotides -59 to -53) of the human PES-2 gene markedly reduced the promoter activity (25%) of the PES-2 gene after combined treatment with LPS and TPA, although single destruction of the NF-IL6 site or the CRE slightly reduced the promoter activity (60 or 90%, respectively). Moreover, cotransfection experiments showed that a trans-acting factor, CCAAT enhancer binding protein (C/EBPdelta), which binds to both the NF-IL6 site and the CRE, increased the promoter activity of the PES-2 gene mainly through the CRE. C/EBPdelta mRNA was rapidly induced by LPS. Collectively, these results suggest that transcription of the PES-2 gene in vascular endothelial cells is regulated through combination of the NF-IL6 site and the CRE and that C/EBPdelta functions as one of the trans-acting factors.

19/3,AB/63 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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06175621 EMBASE No: 1995199102
Lupus anticoagulants: Clinic, pathophysiology, diagnosis and therapy
LUPUS-ANTIKOAGULANS: KLINIK, PATHOPHYSIOLOGIE, DIAGNOSTIK UND THERAPIE
Potsch B.; Madlener K.
Kerckhoff-Klinik, Abteilung Hamostaseologie, Transfusionsmedizin, Sprudelhof 11,D-61231 Bad Nauheim Germany
Hamostaseologie (HAMOSTASEOLOGIE) (Germany) 1995, 15/2 (100-104)
CODEN: HAEMD ISSN: 0720-9355
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH;
GERMAN

Lupus anticoagulants (LA) are autoantibodies directed against negatively charged phospholipids. The presence of LA is closely associated with the occurrence of arterial and venous thrombosis, thrombocytopenia, and recurrent abortion. However, the nature of the association between LA and these clinical events is unknown. Competition of LA and activated protein C for binding sites on negatively charged phospholipids resulting in an acquired APC dysfunction has been reported by several authors and may be one cause of thrombosis in LA. A recommended system for detecting and confirming LA is to use phospholipid depleted tests such as the Kaolin-Clotting-Time, the Textarin-Ecarin-Ratio, or modified aPTTs to initially screen for LA. An anticoagulant should be subsequently confirmed by failure to correct the defect in a mixture of test and normal plasma or by a relative correction of the LA defect by addition of phospholipids. Patients diagnosed as positive for LA and showing a history of thrombosis should be referred to oral anticoagulation until LA values reach base-line levels.

19/3,AB/64 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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05918666 EMBASE No: 1994331970
Autoantibodies to phospholipid-binding plasma proteins: A new view of lupus anticoagulants and other 'antiphospholipid' autoantibodies
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Blood (BLOOD) (United States) 1994, 84/9 (2854-2867)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

19/3,AB/65 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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05607921 EMBASE No: 1994012173
Hypercoagulable states
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United States
Annals of Internal Medicine (ANN. INTERN. MED.) (United States) 1993, 119/8 (819-827)
CODEN: AIMEA ISSN: 0003-4819
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Purpose: To describe the major pathophysiologic mechanisms underlying inherited and secondary hypercoagulable states and to evaluate the frequency, natural history, diagnosis, and management of the various clinical disorders. Data Sources and Study Selection: Relevant clinical literature obtained from bibliographies in hematology textbooks and from computerized indexes was reviewed. A hypothesis was formed based on this literature review and on recent developments from a number of experimental studies. Data Synthesis: Hypercoagulable states include various inherited as well as acquired clinical disorders characterized by an increased risk for thromboembolism. Primary hypercoagulable states include relatively rare inherited conditions that lead to disordered endothelial cell thromboregulation. These conditions include decreased thrombomodulin-dependent activation of activated protein C, impaired heparin binding of antithrombin III, or down-regulation of membrane-associated plasmin generation. The major, inherited, inhibitor disease states include antithrombin III deficiency, protein C deficiency, and protein S deficiency and should be considered in patients who have recurrent, familial, or juvenile deep-vein thrombosis or occlusion in an unusual location such as a mesenteric, brachial, or cerebral vessel. Secondary hypercoagulable states may be seen in many heterogeneous disorders. In many of these conditions, endothelial activation by cytokines leads to loss of normal vessel-wall anticoagulant surface functions with conversion to a proinflammatory thrombogenic phenotype. Important clinical syndromes associated with substantial thromboembolic events include the antiphospholipid syndrome, heparin-induced thrombopathy, the myeloproliferative syndromes, and cancer. Conclusions: Physiologic thromboregulation occurs at the vessel-wall surface. Quantitative and qualitative deficiencies of normal, steady-state endothelial anticoagulant activities are associated with primary hypercoagulable states. Activated endothelial cell surfaces express a thrombogenic phenotype and contribute to secondary or acquired hypercoagulability.

19/3,AB/66 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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05183761 EMBASE No: 1992323995
Blockade of protein C activation reduces microvascular surgical blood loss
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Department of Surgery, Oklahoma Univ. Health Sciences Ctr., Oklahoma City, OK 73104 United States
Journal of Surgical Research (J. SURG. RES.) (United States) 1992, 52/6 (560-564)

CODEN: JSGRA ISSN: 0022-4804
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Protein C is a natural anticoagulant glycoprotein which prevents intravascular clot formation. Protein C functions as an anticoagulant when converted to an active serine protease (activated protein C). Activated protein C is formed at the site of the endothelial injury in response to blood clotting and helps limit the size of blood clots. We tested the hypothesis that by temporarily blocking the activation of intrinsic protein C, we could reduce subsequent surgical blood loss from a microvascular surgical wound. The formation of activated protein C was blocked systemically by intravenous administration of a monoclonal antibody (HPCinf 4) which binds to circulating protein C and prevents its conversion to activated protein C. Domestic pigs were blindly pretreated with intravenous HPCinf 4 or saline then underwent partial-thickness skin graft harvesting to create a reproducible microvascular wound. Blood loss was measured from each wound and the hemostatic effect of protein C blockade was compared to intravenous saline alone as well as to topical thrombin or thromboplastin. We found that blocking the activation of protein C significantly ($P = 0.005$) reduces surgical blood loss in this model by 27% compared to saline control animals. Intravenous HPCinf 4 performed equally as well as topical thrombin or tissue thromboplastin. In addition, topical thrombin acted synergistically with HPCinf 4 to reduce blood loss an additional 44% ($P = 0.01$) as compared to intravenous HPCinf 4 or topical thromboplastin alone. Autopsies performed 1 week after HPCinf 4 treatment showed no evidence of systemic thrombosis resulting from the protein C blockade. This study reveals that blocking the formation of the natural anticoagulant, activated protein C prior to surgery provides a systemic means of reducing capillary bleeding from vascular beds.

19/3,AB/67 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
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05175813 EMBASE No: 1992316047
Calcium ionophore A23187 induces expression of the growth arrest and DNA damage inducible CCAAT/enhancer-binding protein (C/EBP)-related gene, gadd153. Casup 2sup + increases transcriptional activity and mRNA stability
Bartlett J.D.; Luethy J.D.; Carlson S.G.; Sollott S.J.; Holbrook N.J.
Laboratory of Molecular Genetics, National Institute on Aging, Baltimore, MD 21224 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1992, 267/28 (20465-20470)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

gadd153 is a CCAAT/enhancer-binding protein (C/EBP)-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Casup 2sup + might play a role in regulating expression of gadd153. We have demonstrated that treatment of HeLa cells with the calcium ionophores A23187 and ionomycin leads to the induction of gadd153 mRNA. The induction was rapid; increases in mRNA were detected by 90 min of treatment, and near maximum levels were achieved within 5-h exposure to A23187. Elevated mRNA levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression. Buffering intracellular and extracellular Casup 2sup + by combined treatment with BAPTA-AM (acetoxymethyl ester form of bis(aminophenoxy)ethane N,N'-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA by A23187. In addition, these treatments prevented the induction of gadd153 mRNA in response to the DNA damaging agent methyl methanesulfonate. We conclude that intracellular Casup 2sup + plays a role in regulating gadd153 expression. More specifically, Casup

2sup + likely plays a role in the induction of gadd153 mRNA following DNA damage.

19/3,AB/68 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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05165967 EMBASE No: 1992306200
slow border cells, a locus required for a developmentally regulated cell migration during oogenesis, encodes drosophila C/EBP
Montell D.J.; Rorth P.; Spradling A.C.
Department of Biological Chemistry, Johns Hopkins Univ. Sch. of Medicine, Baltimore, MD 21205 United States
Cell (CELL) (United States) 1992, 71/1 (51-62)
CODEN: CELLB ISSN: 0092-8674
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

During *Drosophila* oogenesis six to ten follicle cells, the border cells, undergo a dramatic and stereotypic migration through the developing egg chamber. We identified four independent P element insertion mutations that specifically blocked border cell migration. They defined a single, novel locus that was named slow border cells (slbo), because hypomorphic alleles caused delayed onset of the migration. Laser ablation of the border cells, or failure of their migration, caused improper morphogenesis of the micropyle, the eggshell structure through which the sperm enters at fertilization. The slbo locus was found to encode a product homologous to the CCAAT/enhancer-binding protein (C/EBP), a basic region-leucine zipper transcription factor. *Drosophila* C/EBP may be required for the expression of gene products mediating border cell migration.

19/3,AB/69 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE
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05113728 EMBASE No: 1992253944
The possible inhibitory role of the leucine-zipper DNA binding protein (C/EBP)-related gene, gadd153, in the regulation of hepatic gene expression after sepsis
Barke R.A.; Brady P.S.; Roy S.; Charboneau R.; Brady L.J.
Department of Surgery, Minneapolis VA Medical Center, 1 Veterans Dr., Minneapolis, MN 55417 United States
Surgery (SURGERY) (United States) 1992, 112/2 (412-418)
CODEN: SURGA ISSN: 0039-6060
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background. The leucine-zipper c-fos has been implicated in the regulation of gene expression. We investigated the possible role of c-fos in the regulation of hepatic gene expression after sepsis. Based on previous data demonstrating that sepsis inhibits hepatic gene expression of carnitine palmitoyltransferase (CPT), we hypothesized that c-fos may play a role in the inhibition of CPT gene expression after sepsis. Methods. We studied c-fos gene expression after peritoneal sepsis induced by cecal ligation and puncture (CLP) or sham-CLP. To investigate the possible inhibitory role of c-fos on CPT gene transcription, we investigated the effect of c-fos on c-jun-driven CPT promoter-chloramphenicol acyltransferase reporter gene expression in a HepG2 hepatoma cell cotransfection model. To investigate the possible role of cyclic adenosine monophosphate (cAMP) in the regulation of c-fos in vivo, we treated either the sham-CLP group or the CLP group with either vehicle or cAMP. Results. Peritoneal sepsis in the rat model resulted in a four-fold increase in hepatic c-fos mRNA and c-fos protein. In the cotransfection model, c-fos significantly inhibited c-jun-induced chloramphenicol acyltransferase activity. Treatment with cAMP resulted in a 50% decrease in c-fos protein in either the sham-CLP or CLP group. Conclusions. We conclude that (1) sepsis increases hepatic c-fos transcription and translation, (2) c-fos inhibits c-jun-induced CPT gene expression, and (3) cAMP probably does not directly mediate the increase in c-fos after sepsis.

19/3,AB/70 (Item 16 from file: 73)

DIALOG(R)File 73:EMBASE
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05032789 EMBASE No: 1992173005

Testing and characterizing enzymes and membrane-bound carrier proteins acting on amphipathic ligands in the presence of bilayer membrane material and soluble binding protein. Application to the uptake of oleate into isolated cells

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Laboratory of Hepatology, Faculty of Medicine, Katholieke Universiteit Leuven, Gasthuisberg, 3000-Leuven Belgium
Biochemical Journal (BIOCHEM. J.) (United Kingdom) 1992, 284/2 (353-361)
CODEN: BIJOA ISSN: 0264-6021
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

1. A multiphasic modelling approach (Heirwegh, Meuwissen, Vermeir and De

Smedt (1988) Biochem. J. 254, 101-108) is applied to systems containing poorly water-soluble amphipathic reactants, membrane material, soluble binding protein and acceptor protein (enzyme or membrane-bound carrier protein). 2. The field of application is constrained by the assumptions (i) that the amount of acceptor-bound substrate is small compared with the total amount and (ii) that all preceding chemical reactions and steps of mass transport are rapid compared with the chemical change monitored. 3. Initial-rate formulae for systems in which an acceptor interacts with unbound or protein-bound ligand are given. The saturation curves are near-hyperbolic or sigmoidal, depending both (i) on the form of ligand (unbound or protein-bound) acted upon by the acceptor and (ii) on whether the assays are performed at constant concentration of soluble

protein binding site or at constant substrate/binding-site molar ratio R(s). 4. Several diagnostic features permit unequivocal distinction between acceptor action on unbound or protein-bound substrate. In the former case, saturation curves, run at the same constant concentration of one of several binding proteins of increasing binding affinity, will show progressively increasing inhibition, the shape changing from near-hyperbolic at $K(m)' < Kinf\ 1'$ to sigmoidal at $K(m)' > Kinf\ 1'$. $K(m)'$ is the effective Michaelis constant of the acceptor and $Kinf\ 1'$ the effective dissociation constant of the binding sites of the soluble protein (for the sites with the higher binding affinity, if several classes of binding site are present on the protein). Alternatively, the maximum velocity obtained at constant $R(s) \leq 1$ should increase hyperbolically with $R(s)/(1-R(s))$ for a binding protein with a single class of binding site. The formula that applies when the binding protein contains two classes of independent binding site is also available. When the acceptor acts on protein-bound ligand, the maximum velocity obtained at constant binding-protein concentration, $C(p)$, increases hyperbolically with $C(p)$. 5. Application of these and additional criteria to initial-rate data on the uptake of oleate into isolated cells supports a mechanism of carrier-mediated uptake of the unbound ligand and allows one to clarify some observations that hitherto had been poorly explained. 6. The influence of soluble binding protein on the reaction and substrate specificities of ligand/acceptor interaction is also discussed. 7. In its present state, data for 'double binding-protein systems' generally requires separate determination of the binding parameters of the soluble binding protein. Possible designs for direct application of data-fitting procedures are briefly discussed. 8. Details about the units used and about the derivation of ligand distribution functions, kinetic formulae and their properties, and formulae for interconversion of parameter values to various concentration scales have been deposited as Supplementary Publication SUP 50169 (16 pages) at the British Library Document Supply Centre, Boston Spa, Wetherby, West Yorkshire LS23 7BQ, U.K., from whom copies can be obtained on the terms indicated in Biochem. J. (1992) 281, 5.

19/3,AB/71 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE
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04928181 EMBASE No: 1992068397

A phosphorylation site located in the NHinf 2-terminal domain of c-Myc increases transactivation of gene expression

Seth A.; Alvarez E.; Gupta S.; Davis R.J.
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Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1991, 266/35 (23521-23524)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The c-myc gene encodes a sequence-specific DNA-binding protein that forms leucine zipper complexes and can act as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Sersup 6sup 2 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I.C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R.J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34(cdc2). We report that serum treatment of cells results in a marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutation at the site of growth factor-stimulated phosphorylation (Sersup 6sup 2) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

19/3,AB/72 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08935719 97058628

Effects of perturbations of the hypothalamic-pituitary-adrenal axis on the acute phase response: altered C/EBP and acute phase response gene expression in lipopolysaccharide-treated rats.
Eastman HB; Fawcett TW; Udelsman R; Holbrook NJ
Gene Expression and Aging Section, National Institute on Aging, Baltimore, Maryland 21224, USA.
Shock (UNITED STATES) Oct 1996; 6 (4) p286-92, ISSN 1073-2322

Journal Code: CAE
Languages: ENGLISH
Document type: JOURNAL ARTICLE

In this study, we investigated the influence of long term perturbations of the hypothalamic-pituitary-adrenal axis on the acute phase response elicited following lipopolysaccharide (LPS) challenge in rats. Specifically, we examined the effects of either long term absence of glucocorticoids (adrenalectomized rats treated with placebo chronic release pellets) or extended exposure to pharmacologic levels of glucocorticoids (adrenalectomized rats treated with dexamethasone chronic release pellets) on the expression of selected acute phase proteins and various members of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors. Both hypothalamic-pituitary-adrenal axis manipulations resulted in a reduction of the acute phase response as assessed by the LPS-mediated induction of acute phase proteins and C/EBP gene expression, with dexamethasone exhibiting a greater inhibitory effect than adrenalectomy. Induction of hemopexin, alpha 1-acid glycoprotein, alpha 2-macroglobulin, GADD153, C/EBP beta, and C/EBP delta mRNAs by LPS were all abolished in dexamethasone-treated rats. These findings have direct implications for patients undergoing chronic high dose glucocorticoid therapy.

19/3,AB/73 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

08781649 96362667

Modulation of myosin filament organization by C-protein family members.
Seiler SH; Fischman DA; Leinwand LA

Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA.

Molecular biology of the cell (UNITED STATES) Jan %%%1996%%%, 7 (1)

p113-27, ISSN 1059-1524 Journal Code: BAU

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Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have analyzed the interactions between two types of sarcomeric proteins: myosin heavy chain (MyHC) and members of an abundant thick filament-associated protein family (myosin-binding protein; MyBP). Previous work has demonstrated that when MyHC is transiently transfected into mammalian nonmuscle COS cells, the expressed protein forms

spindle-shaped

structures consisting of bundles of myosin thick filaments. Co-expression of MyHC and MyBP-C or -H modulates the MyHC structures, resulting in

dramatically longer cables consisting of myosin and MyBP encircling the nucleus. Immunoelectron microscopy indicates that these cable structures are more uniform in diameter than the spindle structures consisting solely of MyHC, and that the myosin filaments are compacted in the presence of MyBP. Deletion analysis of MyBP-H indicates that cable formation is dependent on the carboxy terminal 24 amino acids. Neither the MyHC spindles

nor the MyHC/MyBP cables associate with the endogenous actin cytoskeleton

of the COS cell. While there is no apparent co-localization between these structures and the microtubule network, colchicine %%%treatment%%% of the

cells promotes the formation of longer assemblages, suggesting that cytoskeletal architecture may physically impede or regulate polymer formation/extension. The data presented here contribute to a greater understanding of the interactions between the MyBP family and MyHC, and

provide additional evidence for functional homology between MyBP-C and MyBP-H.

19/3,AB/74 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08764339 96336108

Growth hormone-binding protein related immunoreactivity is regulated by the degree of insulinopenia in diabetes mellitus.

Kratzsch J; Kellner K; Zilkens T; Schmidt-Gayk H; Selisko T; Scholz GH

Department of Clinical Chemistry, University of Leipzig, Germany.

Clinical endocrinology (ENGLAND) Jun %%%1996%%%, 44 (6)

p673-8, ISSN

0300-0664 Journal Code: DCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

OBJECTIVE: Derangements in the GH/IGF axis are common in patients with

diabetes mellitus. In insulin-dependent diabetes mellitus (IDDM), these disturbances seem to be due to a partial defect in GH action on its own receptor or via a post-receptor defect. In non-insulin-dependent diabetes mellitus (NIDDM), data are limited, and the regulation of the GH receptor (GHR) remains unclear. However, animal studies with diabetic rats demonstrated that the GHR density may be influenced by insulin disposal at the hepatocyte. With respect to this hypothesis we studied the relation between peripheral insulin status and the serum GH-binding protein (GHBP), which reflects indirectly the GHR density in the tissues. Patients with IDDM were compared to a NIDDM group as well as to a group of healthy

subjects. DESIGN AND PATIENTS: Basal blood samples for the determination of

serum GHBP, GH, and IGF-I were obtained from patients with IDDM (n = 27),

subjects with NIDDM (n = 112) and healthy controls (n = 42). Insulin, proinsulin, C-peptide and IGF-binding protein 1 (IGFBP-1) serum levels were used to estimate the insulin status in diabetic patients. RESULTS: GHBP serum levels were significantly lower in patients with IDDM than in either NIDDM or controls (P < 0.001). Conversely, the IGF-I levels were reduced in

both groups of diabetics. A subgroup of hypoinsulinaemic NIDDM patients showed significantly decreased GHBP concentrations (P < 0.05) compared to

the NIDDM sub-group with hyperinsulinaemia. Furthermore, GHBP levels were significantly decreased in insulin-%%treated%% patients with NIDDM

compared to either non-insulin-requiring subjects or normal controls (P < 0.05). A significant direct relation was found between levels of GHBP and total insulin dose (P < 0.01) in patients with IDDM. In the NIDDM group, GHBP was correlated with proinsulin (P < 0.001), C-peptide (P < 0.01), Insulin (P < 0.05) and inversely with IGFBP-1 (P < 0.001). Multiple linear regression analysis indicated a significant contribution of proinsulin and IGFBP-1 to the variation of GHBP. CONCLUSIONS: Decreased GHBP levels in

IDDM as well as in NIDDM correlate with insulinopenia. Since the degree of

insulinopenia depends on the capability of the beta-cells to secrete proinsulin, C-peptide and insulin, we hypothesize that these hormones at least partially influence the serum level of GHBP. Low GHBP levels may reflect a reduced GH receptor density and a concomitant GH insensitivity, which leads to an impaired IGF generation in insulin-deficient patients.

19/3,AB/75 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

08499010 96162443

The protein tyrosine kinase Fyn activates transcription from the HIV promoter via activation of NF kappa B-like DNA-binding proteins.

Hohashi N; Hayashi T; Fusaki N; Takeuchi M; Higurashi M; Okamoto T; Semba

K; Yamamoto T

Department of Oncology, University of Tokyo, Japan.

International immunology (ENGLAND) Nov %%%1995%%%, 7 (11)

p1851-9,

ISSN 0953-8178 Journal Code: AYS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Protein tyrosine kinase p59fyn (Fyn) associates with the TCR-CD3

complex,

which suggests that Fyn plays a significant role in the signal transduction involving TCR complex. In addition to cellular genes, viral promoters such as the HIV long terminal repeat (LTR) are also activated upon T cell

activation. To elucidate the functional significance of Fyn in the expression of viral promoters, we transfected a Fyn-expression vector together with a reporter plasmid containing the chloramphenicol acetyltransferase gene driven by HIV LTR into a human T cell line, Jurkat. In this assay, Fyn stimulated the promoter in HIV LTR when the transfected cells were %%%treated%%% with both concanavalin A and PMA as an

antigen-mimic stimulation. This activation required the intact SH2 domain of Fyn. Mutational analysis of HIV LTR showed that the NF kappa B binding

sites were responsible for this effect. Electrophoretic mobility shift assays and UV cross-linking experiments showed that activation of T cells by anti-CD3 antibody induced four kappa B-binding proteins (50, 60, 65 and 100 kDa) in Fyn-overexpressing cells more efficiently than in the parental cells. Our results suggested that Fyn was able to regulate expression of a subset of genes via kappa B-binding proteins upon T cell activation.

19/3,AB/76 (Item 5 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

07974835 94327567

Induction of GADD153, a CCAAT/enhancer-%%binding%%%

%%protein%%%

%%C%%/EBP)-related gene, during the acute phase response in

rats.

Evidence for the involvement of C/EBPs in regulating its expression

[published erratum appears in J Biol Chem 1995 Jun 16;270(24):14842]

Sylvester SL; ap Rhys CM; Luethy-Martindale JD; Holbrook NJ

Section on Gene Expression and Aging, National Institute on Aging, Baltimore, Maryland 21224.

Journal of biological chemistry (UNITED STATES) Aug 5

1994, 269

(31) p20119-25, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

CCAAT/enhancer-binding proteins (C/EBPs) comprise a homologous group of

transcriptional regulators that control liver and fat differentiation and are involved in regulating the expression of acute phase reactants during the host response to inflammation. GADD153, a unique member of the C/EBP family, has been proposed to act as a dominant negative inhibitor of other C/EBPs, but little is known about its expression in liver or its role in the processes described above. We have examined its expression during the acute phase response (APR) and have shown that like C/EBP beta and C/EBP delta, GADD153 mRNA is markedly induced in livers of rats

with lipopolysaccharide to initiate the APR. Interestingly, its induction is temporally delayed relative to that of C/EBP beta and C/EBP delta but is similar to that of acute phase reactants shown to be regulated by C/EBPs. Footprint analysis of the GADD153 promoter showed binding of proteins in liver extracts of both untreated and lipopolysaccharide-injected rats to a putative C/EBP regulatory site. Gel shift analysis showed that although present constitutively, binding activity was increased in extracts from lipopolysaccharide-treated animals. Both C/EBP alpha and C/EBP beta

were shown to contribute to the binding activity with the contribution by C/EBP beta increasing during the APR. Support for the functional role of this C/EBP-binding site and its interaction with C/EBPs in regulating GADD153 expression was obtained with cultured HepG2 hepatoma cells in which overexpression of C/EBP beta was found to transactivate expression of a plasmid containing the GADD153 promoter linked to a reporter gene.

These findings suggest that the GADD153 gene is itself regulated by C/EBPs during the host response to inflammation and that GADD153 is likely to contribute to the regulation of other genes whose expression is altered during the APR.

19/3,AB/77 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

07708175 94109099

Insulin therapy increases low plasma growth hormone binding protein in children with new-onset type 1 diabetes.

Arslanian SA; Menon RK; Gierl AP; Heil BV; Foley TP Jr
Division of Pediatric Endocrinology, Metabolism and Diabetes Mellitus, Children's Hospital, University of Pittsburgh, PA.

Diabetic medicine (ENGLAND) Nov 1993; 10 (9)

p833-8, ISSN

0742-3071 Journal Code: DME

Contract/Grant No.: 5 MO1-RR00086-25 (GC RC), RR, NCRR; R29 HD27503-02, HD, NICHD

Languages: ENGLISH

Document type: JOURNAL ARTICLE

This study was undertaken (1) to evaluate growth hormone binding protein (GHBP) levels in newly diagnosed patients with Type 1 diabetes before

and after insulin therapy and (2) to determine the relationship of GHBP to glycaemic control, C-peptide level and blood pH. GHBP, expressed as a percentage of (125I)GH bound, was determined in 33 patients with Type 1 diabetes (M/F = 19/14, 12.3 +/- 0.4 years) before (day 0), after 5 days (day 5) and after 3 months (month 3) of insulin therapy. At day 0, GHBP was lower in Type 1 diabetes compared with 38 matched healthy control subjects (3.9 +/- 0.4 vs 8.2 +/- 0.4%, p < 0.001). There was no significant improvement in GHBP at day 5 (4.4 +/- 0.3%). At month 3, GHBP increased to

(6.0 +/- 0.4%, p < 0.001 vs day 0), but was still lower than controls, p < 0.001. At day 0 GHBP correlated with BMI (r = 0.50, p = 0.001), blood glucose (r = -0.43 p = 0.006) and pH (r = 0.48, p = 0.004), but not HbA1c. GHBP at month 3 correlated with day 0 C-peptide (r = 0.41, p = 0.02). Thus, (1) circulating GHBP is low in newly diagnosed patients with Type 1

diabetes, and increases after 3 months of insulin therapy but does not normalize and (2) the severity of biochemical derangement and residual

beta-cell function at diagnosis may determine GHBP status and its recovery. We conclude that insulin is an important modulator of GH binding protein in newly diagnosed children with Type 1 diabetes.

19/3,AB/78 (Item 7 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

07375498 92084631

A phosphorylation site located in the NH2-terminal domain of c-Myc increases transactivation of gene expression.

Seth A; Alvarez E; Gupta S; Davis RJ
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester 01605.

Journal of biological chemistry (UNITED STATES) Dec 15

1991, 266

(35) p23521-4, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: GM37845, GM, NIGMS; CA39240, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The c-myc gene encodes a sequence-specific

DNA-binding

protein (c-Myc) that forms leucine zipper complexes and can act

as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Ser62 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I.C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R. J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34cdc2. We report that serum treatment of cells results in a

marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutation at the site of growth factor-stimulated phosphorylation (Ser62) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

19/3,AB/79 (Item 8 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

07134005 93015930

Calcium ionophore A23187 induces expression of the growth arrest and DNA

damage inducible CCAAT/enhancer-binding

protein (C/EBP)

-related gene, gadd153. Ca2+ increases transcriptional activity and mRNA stability.

Bartlett JD; Luethy JD; Carlson SG; Sollott SJ; Holbrook NJ
Laboratory of Molecular Genetics, National Institute on Aging, Baltimore, Maryland 21224.

Journal of biological chemistry (UNITED STATES) Oct 5

1992, 267

(28) p20465-70, ISSN 0021-9258 Journal Code: HIV

Languages: ENGLISH

Document type: JOURNAL ARTICLE

gadd153 is a CCAAT/enhancer-binding

protein (C/EBP)

-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Ca2+ might play a role in regulating expression of gadd153. We have demonstrated that treatment of HeLa cells with the calcium ionophores A23187

and ionomycin leads to the induction of gadd153 mRNA. The induction was rapid;

increases in mRNA were detected by 90 min of treatment, and near

maximum levels were achieved within 5-h exposure to A23187. Elevated

mRNA levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression.

Buffering intracellular and extracellular Ca²⁺ by combined
 %%%treatment%%%
 with BAPTA-AM (acetoxymethyl ester form of
 bis(aminophenoxy)ethane
 N,N-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA
 by
 A23187. In addition, these %%%treatments%%% prevented the induction
 of
 gadd153 mRNA in response to the DNA damaging agent methyl
 methanesulfonate.
 We conclude that intracellular Ca²⁺ plays a role in regulating gadd153
 expression. More specifically, Ca²⁺ likely plays a role in the induction of
 gadd153 mRNA following DNA damage.

19/3,AB/80 (Item 9 from file: 155)
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 2000 Dialog Corporation. All rts. reserv.

06976371 92041747
 Synthesis of protein C in human umbilical vein endothelial cells.
 Tanabe S; Sugo T; Matsuda M
 Institute of Hematology, Jichi Medical School, Tochigi.
 Journal of biochemistry (JAPAN) Jun %%%1991%%%, 109 (6) p924-8,
 ISSN
 0021-924X Journal Code: HIF
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 By monitoring the activation of protein C and the regulation of factor
 Xa-catalyzed thrombin formation by the activated protein C (APC) on the
 surface of human umbilical vein endothelial cells (HUVEC), we found that
 functional protein C was synthesized in cultured HUVEC and expressed
 thereon in the presence of vitamin K. Furthermore, without exogenously
 added protein S, time-dependent and saturable accumulation of APC (20
 fmol
 APC/10(5) cells) on the surface of HUVEC was observed. During
 prothrombin
 activation by the complex of membrane-bound factor Xa and endogenous
 factor
 Va formed on the surface of HUVEC, APC was generated, and the rate of
 thrombin formation decreased. %%%Treatment%%% of HUVEC with an
 antibody
 that inhibits the APC-catalyzed inactivation of endogenous factor Va
 clearly quenched the activity of surface-associated APC. Immunostaining of
 HUVEC with a horseradish peroxidase (HRP)-conjugated antibody that
 solely
 recognizes human protein C confirmed the presence of protein C on the
 surface of HUVEC. Northern blot analysis revealed that an about 1.8 kb
 mRNA
 species derived from HUVEC was hybridized with 32P-labeled protein C
 cDNA,
 as in the case of those from HepG2, which are known to synthesize normal
 protein C. The increase in the amount of protein C mRNA in HUVEC in
 parallel with cell growth provided supporting evidence for the synthesis of
 protein C during the culture of HUVEC. These results indicate that blood
 coagulation is regulated by endogenously generated and activated protein C,
 together with or without protein S, through inactivation of factor Va on
 the surface of endothelial cells.

19/3,AB/81 (Item 10 from file: 155)
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 2000 Dialog Corporation. All rts. reserv.

06919643 91266936
 Different glycoforms of human thrombomodulin. Their
 glycosaminoglycan-dependent modulatory effects on thrombin inactivation
 by
 heparin cofactor II and antithrombin III.
 Koyama T; Parkinson JF; Sie P; Bang NU; Muller-Berghaus G; Preissner
 KT
 Haemostasis Research Unit, Kerckhoff-Klinik, Bad Nauheim, Federal
 Republic of Germany.
 European journal of biochemistry (GERMANY) Jun 15 %%%1991%%%,
 198 (3)
 p563-70, ISSN 0014-2956 Journal Code: EMZ
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE

The relationship between thrombomodulin-associated O-linked
 glycosaminoglycans (GAGs) and the exogenous GAGs heparin or dermatan
 sulfate
 was studied in the inhibition of thrombin by antithrombin III (AT III) or
 heparin cofactor II (HC II). Both rabbit thrombomodulin (TM) and two
 glycoforms (a high-Mr form containing GAGs and a low-Mr form lacking
 the
 majority of O-linked GAGs) of a recombinant human TM deletion
 mutant
 (rec-TM) were used. The rapid inactivation of thrombin by HC II in the
 presence of dermatan sulfate was prevented by both the high-Mr rec-TM
 and
 the rabbit TM. In contrast, both rabbit TM %%%treated%%% with
 chondroitin
 ABC lyase to remove O-linked GAGs and the low-Mr form of rec-TM had
 only
 weak protecting effects. In the absence of exogenous dermatan sulfate,
 thrombin inhibition by a high concentration of HC II was slightly
 accelerated by the high-Mr form of rec-TM but protected by rabbit TM.
 When
 thrombin inhibition by AT III in the presence of heparin was studied, both
 high-Mr rec-TM and rabbit TM again invoked a similar reduction of
 inactivation rates, whereas in the absence of exogenous heparin, both
 high-Mr forms accelerated thrombin inhibition by AT III. The diverse
 reactivities of various forms of TM towards HC II and AT III were also
 observed during protein C activation by the thrombin-TM complex. These
 results suggest that thrombin activity at the vessel wall or in fluid phase
 may undergo major kinetic modulations depending on the type of protease
 inhibitor, the presence or absence of exogenous GAGs and the glycosylation
 phenotype of TM. The dependence of TM anticoagulant function on the
 presence of an intrinsic GAG moiety suggests that variant glycoforms of
 this endothelial cell cofactor may be expressed differently in a species-
 organ-, or tissue-specific manner as a means to regulate TM function in
 diverse vasculatures.

19/3,AB/82 (Item 11 from file: 155)
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 2000 Dialog Corporation. All rts. reserv.

06058869 87296899
 [Protein C, protein S]
 Proteine C, proteine S.
 Guillin MC; Bezeaud A
 Annales de biologie clinique (FRANCE) %%%1987%%%, 45 (2)
 p184-90,
 ISSN 0003-3898 Journal Code: 4ZS
 Languages: FRENCH Summary Languages: ENGLISH
 Document type: JOURNAL ARTICLE : English Abstract
 Protein C is a potent inhibitor of blood coagulation, and, in addition,
 appears to be a profibrinolytic agent. In a first step, protein C must be
 converted to a serine protease. This activation is catalyzed by a complex
 formed between thrombin and thrombomodulin, an endothelial cell surface
 protein. Activated protein C exhibits its anticoagulant activity through
 the proteolytic inactivation of two blood coagulation cofactors, factors Va
 and VIIIa. This reaction requires phospholipids, originating from platelets
 or endothelial cells, and a cofactor protein, protein S. Protein S enhances
 the %%%binding%%% of activated %%%protein%%% %%%C%%% to
 phospholipids. In
 addition, activated protein C stimulates fibrinolysis, through the
 inactivation of the tissue plasminogen activator (tPA) inhibitor. An
 isolated constitutional, quantitative or qualitative, protein C or protein
 S deficiency increases the risk of thrombosis, the clinical features are
 different in the rare cases of homozygous protein C deficiency (neonatal
 purpura fulminans) or in the heterozygous patients (recurrent venous
 thrombosis in young adults). Acquired deficiency in protein C and S had
 been observed in liver disease, during vitamin K antagonists or
 L-Asparaginase %%%treatment%%%, and in disseminated
 intravascular
 coagulation.

19/3,AB/83 (Item 12 from file: 155)
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 2000 Dialog Corporation. All rts. reserv.

05763963 89278077
 Monoclonal antibodies to human thrombomodulin whose binding is

calcium
dependent.

Kimura S; Nagoya T; Aoki N
Tokyo Research Institute, Kowa Ltd.
Journal of biochemistry (JAPAN) Mar 1989; 105 (3)
p478-83.

ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH

Document type: JOURNAL ARTICLE

Four monoclonal antibodies to human thrombomodulin were characterized.

Binding of two of these antibodies was dependent on the presence of calcium ions, and approximately 5 mM calcium was required for their maximum binding. These two antibodies inhibited the binding of thrombin to thrombomodulin, thereby inhibiting activation of protein C catalyzed by thrombin-thrombomodulin complex. These two antibodies bind to a major active fragment formed by limited proteolytic digestions of thrombomodulin with elastase and trypsin, suggesting that the antibodies bind to the thrombin-binding site (or its vicinity) located in the epidermal growth factor (EGF)-homology domain. One of the other calcium-independent antibodies also inhibited the binding of thrombin and the activation of protein C, but the inhibition was very weak and was observed only when the antibody was present in a molar excess over thrombomodulin. This antibody did not bind to the protease digests of thrombomodulin. Another calcium-independent antibody did not inhibit either thrombin binding or protein C activation, but bound to the active fragment of protease digests, suggesting that the antibody binds to a region other than the thrombin-binding site in the EGF-homology domain. These observations suggest that thrombomodulin undergoes a calcium-dependent conformational change which may occur in proximity to a

thrombin-binding site located in the EGF-homology domain.

19/3,AB/84 (Item 13 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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05599344 90028784

Discrimination of normal and abnormal prothrombin and protein C in plasma using a calcium ion-inhibited monoclonal antibody to a common epitope on several vitamin K-dependent proteins.

Church WR; Bhushan FH; Mann KG; Bovill EG

Department of Biochemistry, College of Medicine, University of Vermont, Burlington 05405.

Blood (UNITED STATES) Nov 15 1989; 74 (7)

p2418-25, ISSN

0006-4971 Journal Code: A8G

Contract/Grant No.: HL35058, HL, NHLBI; HL24804, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Vitamin K deficiency or administration of vitamin K antagonists results in the biosynthesis of abnormal des-gamma-carboxy forms of the vitamin K-dependent proteins. Monoclonal antibody H-11 binds several vitamin K-dependent proteins at a determinant that includes the first two residues of gamma-carboxyglutamic acid. Antibody H-11 binds fully carboxylated prothrombin and protein C in the presence of EDTA but binding is inhibited by the divalent metal ions, calcium, magnesium, and manganese. By contrast, des-gamma-carboxy prothrombin and protein C bind to antibody H-11 the same in the presence of EDTA or calcium ion. Antibody H-11 thus

appears to bind a conserved antigenic site containing gamma-carboxyglutamic acid that in the presence of divalent metal ion undergoes a conformational transition. This ability of antibody H-11 to bind des-gamma-carboxy prothrombin and protein C in the presence of calcium ion allowed the development of an immunoassay for these proteins in plasma. Prothrombin and

protein C from stably anticoagulated individuals receiving warfarin were characterized by their ability to bind antibody H-11 in the presence of calcium ion. Binding of prothrombin and protein C to antibody H-11 in the presence of calcium correlated temporally with warfarin administration. The inability of calcium ion to inhibit binding of antibody H-11 to abnormal prothrombin and protein C in plasma suggests that the circulating forms of both proteins following warfarin administration cannot undergo the metal ion-dependent conformational transition that includes sequence residues 1

through 12.

19/3,AB/85 (Item 14 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

05070140 87299786

Immunoaffinity purification of protein C by using conformation-specific monoclonal antibodies to protein C-calcium ion complex.

Nakamura S; Sakata Y

Biochimica et biophysica acta (NETHERLANDS) Aug 13

1987; 925 (2)

p85-93, ISSN 0006-3002 Journal Code: A0W

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We isolated protein C from a barium citrate-adsorbed fresh plasma and human factor IX concentrate by immunoaffinity chromatography on a column of

Sepharose coupled with monoclonal antibodies to protein C. The antibodies used were conformation-specific monoclonal antibodies to the calcium-induced structure of protein C. Protein C was

bound to antibodies coupled with Sepharose in the presence of calcium

ions and was eluted with EDTA. This immunopurification resulted in a 13,000-fold purification of the fully functional zymogen from plasma. The immunoaffinity-isolated protein C was found to have higher amounts of single-chain protein C than conventionally isolated protein C when analyzed by sodium dodecyl sulfate-polyacrylamide gels under reduced conditions. The factor IX concentrate was applied to this Ca²⁺-dependent antibody JTC-3-immobilized Sepharose in the presence of 5 mM CaCl₂, and protein C

with its gamma-carboxyglutamic acid (Gla) domain intact was firstly bound to this column and then eluted by metal chelation with EDTA. When flow-through fractions were applied again in the presence of Ca²⁺ to this column, modified protein C which had lost its N-terminal 42-residue peptide was weakly bound to this column. It was eluted in the absence of Ca²⁺. However, only a low percentage of modified protein C was detectable by an enzyme-linked immunosorbent assay using Ca²⁺-dependent monoclonal antibody

JTC-3 and peroxidase-labeled immunopurified polyclonal antibody. These results indicate that factor IX concentrate has both Gla-domain-intact and Gla-domainless protein C. Moreover, it suggests that Ca²⁺-dependent monoclonal antibody JTC-3 may recognize the coupled conformational change

of protein C induced by the combined effect of Ca²⁺ binding to the Gla domain and to other parts of protein C.

19/3,AB/86 (Item 15 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2000 Dialog Corporation. All rts. reserv.

04365921 84080815

Determination of functional levels of protein C, an antithrombotic protein, using thrombin-thrombomodulin complex.

Comp PC; Nixon RR; Esmon CT

Blood (UNITED STATES) Jan 1984; 63 (1) p15-21, ISSN 0006-4971

Journal Code: A8G

Contract/Grant No.: 7 PO1 HL 30073-01, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Protein C is a vitamin K-dependent plasma protein. Activated protein C is a potent anticoagulant and enhances blood clot lysis. We have developed a functional assay for protein C in human plasma. The measurement of protein C is accomplished by the addition of thrombomodulin, an endothelial-cell-associated cofactor for protein C activation, and thrombin in a 1:1 molar complex. The activated protein C formed in the plasma is immunoabsorbed with goat anti-human protein C IgG-agarose. The immunoabsorbed activated protein C retains the ability to hydrolyze chromogenic substrates, and after unbound plasma proteins are removed by washing, the activated protein C is quantitated by

incubation with the substrate H-D-phe-pip-arg-p-nitroanilide (S-2238).

Normal individuals have functional protein C levels of 3.9-5.9 micrograms/ml, with a mean value of 4.8 micrograms/ml. Individuals

undergoing warfarin anticoagulation and patients with advanced liver diseases have decreased levels, as do certain patients with evidence of intravascular clotting. Functional protein C levels correlate well with immunologic levels of the protein in the patient groups studied. Heparin enhances the rate of activated protein C inhibition, as monitored by recovery of activated protein C by immunoadsorption. A patient with recurrent venous thrombosis and abnormal functional protein C activity, but normal levels of antigen, has been identified.

19/3,AB/87 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0202115 DBA Accession No.: 96-12886 PATENT
DNA encoding human CCAAT/enhancer binding protein - antisense
CCAAT/enhancer %%%binding%% %%%protein%%
%%C%%/EBP-alpha gene
expression from vector for use in hepatoma, etc., gene therapy
AUTHOR: Darlington G J; Wilson D R; Wilde M
CORPORATE SOURCE: Houston, TX, USA.
PATENT ASSIGNEE: Baylor-Coll.Med. %%%1996%%
PATENT NUMBER: US 5545563 PATENT DATE: 960813 WPI
ACCESSION NO.:
96-383675 (9638)
PRIORITY APPLIC. NO.: US 205506 APPLIC. DATE: 940304
NATIONAL APPLIC. NO.: US 205506 APPLIC. DATE: 940304
LANGUAGE: English
ABSTRACT: New DNA (I) encoding human CCAAT/enhancer
%%binding%%
%%protein%% %%%C%%/EBP-alpha is claimed. The DNA
sequence of (I) is
disclosed. Also claimed are: a vector containing (I) for expression in
a mammal cell, especially a hepatic cell; and nucleic acid
complementary to (I), optionally labeled. The vector containing (I),
preferably under the control of a tumor-specific promoter, can be used
for gene therapy of cancer or other diseases. Also disclosed are: using
the vector to inhibit hepatoma proliferation; a method for inducing
proliferation of a hepatic cell, which involves administering a vector
expressing an antagonist of C/EBP-alpha (especially antisense
C/EBP-alpha); a method for %%diagnosis%% of hepatoma using
the
antisense sequence; a method for determining the carcinogenic potential
of a chemical using a transgenic mouse with mutant C/EBP-alpha; and the
transgenic mouse. In an example, C/EBP-alpha gene was isolated from a
phage lambda-gt10 gene bank of genomic DNA from Hep3B2 cells. The
gene
bank was probed with a rat C/EBP-alpha sequence and a clone containing
the whole human C/EBP-alpha gene and 2.2 kb of 5' flanking sequence
was
isolated. (23pp)

19/3,AB/88 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0192541 DBA Accession No.: 96-02734 PATENT
Calcium-binding monoclonal antibody immunoreactive with protein-C -
production by antibody engineering, for application as an antitumor,
and in immunoassay
AUTHOR: Rezaie A; Esmon C T
CORPORATE SOURCE: Oklahoma City, OK, USA.
PATENT ASSIGNEE: Oklahoma-Med.Res.Found. %%%1995%%
PATENT NUMBER: WO 9534652 PATENT DATE: 951221 WPI
ACCESSION NO.:
96-049681 (9605)
PRIORITY APPLIC. NO.: US 259321 APPLIC. DATE: 940610
NATIONAL APPLIC. NO.: WO 95US7372 APPLIC. DATE: 950609
LANGUAGE: English
ABSTRACT: A recombinant calcium-dependent monoclonal antibody
(MAb) is
immunoreactive with an epitope in the activation peptide region of the
heavy chain of protein-C (EC-3.4.21.69) defined by EDQVDPRLIDGK
in
combination with calcium, and inhibits protein-C activation by
thrombin-thrombomodulin. Preferably, the MAb is composed of amino
acids

20-129 or 23-129 of a 129 amino acid specified protein sequence. The
MAb is encoded in part by a 417 bp specified DNA sequence, or bases
58-417 of this, or a 387 bp DNA sequences or bases 67-387 of this. The
MAb is further composed of a carrier, and optionally a cytokine or a
cytokine-inhibitor to coagulate microvasculature in tumors but not in
the absence of the MAb. The MAb may be bound to a detectable label, or
it may be immobilized on a substrate. The MAb is useful in the
%%treatment%% of tumor patients. The immobilized MAb can be
used to
purify protein-C from a biological fluid and in %%diagnostic%%
assays. The MAb contains a DNA sequence from the hypervariable
region
of the HPC-4 antibody, and is useful in mimicking HPC-4
%%protein%%-
%%C%% %%%binding%%. (41pp)

19/3,AB/89 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0189946 DBA Accession No.: 96-00717 PATENT
DNA encoding granulocyte-colony stimulating factor binding region -
recombinant granulocyte-colony stimulating factor receptor binding
region-maltose binding protein fusion protein production by vector
expression in Escherichia coli
CORPORATE SOURCE: Japan.
PATENT ASSIGNEE: Tanpaku-Eng.Res.Inst. %%%1995%%
PATENT NUMBER: JP 7227288 PATENT DATE: 950829 WPI
ACCESSION NO.:
95-331525 (9543)
PRIORITY APPLIC. NO.: JP 93321862 APPLIC. DATE: 931221
NATIONAL APPLIC. NO.: JP 94116252 APPLIC. DATE: 940530
LANGUAGE: JA
ABSTRACT: A DNA encoding a protein derived from the ligand-binding
region
of a granulocyte-colony stimulating factor receptor is claimed. Also
claimed are: (a) a recombinant plasmid containing the DNA under the
control of an Escherichia coli gene expression system; (b) a
recombinant plasmid capable of expressing a fusion protein consisting
of the protein and an E. coli maltose %%binding%%
%%protein%%; (
%%C%%) E. coli transformed with the recombinant plasmids; (d) a
process for producing the protein involving culturing the transformed
E. coli cells and recovering the recombinant product accumulated in the
bacterium; and (e) protein produced by these recombinant methods. The
protein may be used to elucidate the interaction between the
granulocyte-colony stimulating factor receptor and its ligand, as well
as to %%treat%% or prevent granulocyte-colony stimulating
factor-dependent diseases (e.g. leukemia) or abnormalities such as
abnormal growth of granulocytes. (21pp)

19/3,AB/90 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0102336 DBA Accession No.: 90-05027 PATENT
Human Protein-C derivative - chimeric gene cloning and expression, e.g. in
CHO or BHK cell culture; DNA sequence
PATENT ASSIGNEE: Hoechst-Japan %%%1990%%
PATENT NUMBER: EP 354504 PATENT DATE: 900214 WPI
ACCESSION NO.: 90-046218
(9007)
PRIORITY APPLIC. NO.: JP 88179144 APPLIC. DATE: 880809
NATIONAL APPLIC. NO.: EP 89114505 APPLIC. DATE: 890805
LANGUAGE: English
ABSTRACT: A derivative of human Protein-C is claimed, which has the
N-terminal region with gamma-carboxylated Glu residues (Gla domain)
replaced by the Gla domain of cattle Protein-C, or by a sequence with
similar calcium-binding activity and/or enhanced Protein-C activity. A
DNA sequence encoding the protein and a recombinant host cell (e.g. CHO
or BHK cell culture) expressing the gene are also claimed. A DNA
sequence encoding the human Gla domain (e.g. amino acid residues 1-43)
is replaced with the DNA sequence encoding the Gla domain of cattle
Protein-C. The prepro-sequence of human Protein-C may additionally be
replaced with the prepro-sequence of cattle Protein-C, or with the
prepro-sequence of menadione-dependent blood-clotting factors, such as

Factor-X. The hybrid proteins have an increased number of Glu residues (from 9 to 11). By the increased number of gamma-carboxylation sites, enhanced calcium-binding activity of Protein-C and improved activation of Protein-C is obtained. The activated Protein-C inhibits blood-clotting or accelerates fibrinolysis, and is used for treating blood-clotting disorders. (17pp)

19/3,AB/91 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0058193 DBA Accession No.: 87-02541 PATENT
Monoclonal antibody to human protein C
ion at the Gla domain - construction of a hybridoma secreting monoclonal antibody; application to liver disease diagnosis
PATENT ASSIGNEE: Teijin 1986
PATENT NUMBER: EP 205046 PATENT DATE: 861217 WPI
ACCESSION NO.: 86-333583 (8651)
PRIORITY APPLIC. NO.: JP 85124388 APPLIC. DATE: 850610
NATIONAL APPLIC. NO.: EP 86107297 APPLIC. DATE: 860528
LANGUAGE: English
ABSTRACT: A new monoclonal antibody to human protein C does not recognize human protein C not a calcium ion at the Gla domain but recognizes human protein C which does bind a calcium ion at this position. The monoclonal antibody is used for determining or separating human protein C for detection of liver disease. Mice are immunized with human protein C and the spleen cells are extracted and fused with mouse myeloma cells. The resulting hybridoma cells are screened and selected cells isolated and used for the production of desired monoclonal antibody. The mice may be female BALB/c mice which may be immunized e.g. 3 times at 2 wk intervals i.p., then an injection is given i.v. prior to extraction of spleen cells. These are fused with e.g. P3-X63-Ag8-U1 myeloma cells using PEG 1,000 as the preferred fusogen. Hybridomas are cultured in e.g. HAT medium and screened by an ELISA. Hybridoma cells selected may be cloned by limiting dilution and injected into mice for production of ascites. The monoclonal antibodies obtained may be used for isolation of human protein C by binding to a carrier such as Sepharose. (20pp)

19/3,AB/92 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0036148 DBA Accession No.: 85-06937 PATENT
Membrane-bound polypeptide having antigenic determinants - useful for binding to herpes simplex virus
PATENT ASSIGNEE: Genentech 1985
PATENT NUMBER: AU 8432424 PATENT DATE: 850307 WPI
ACCESSION NO.: 85-099048 (8517)
PRIORITY APPLIC. NO.: US 587763 APPLIC. DATE: 840309
NATIONAL APPLIC. NO.: AU 8432424 APPLIC. DATE: 840827
LANGUAGE: English
ABSTRACT: A diagnostic product comprising membrane-bound polypeptide (1) having antigenic determinants capable of specific binding of complementary antibody is new. The (1) is functionally associated with a membrane of a recombinant stable continuous cell line capable of its production. A diagnostic kit is also described.
Membrane-bound (1) are useful as diagnostic agents and are obtained in large amounts by recombinant DNA technology in non-pathogenic form. They may be obtained from a stable continuous cell line. As (1) are especially capable of binding herpes simplex virus specific antibodies, they may also be used in vaccines against the virus or to reduce the effects of an existing infection. The (1) is especially a glycoprotein (C or D) of

herpes simplex virus type 1 or 2 and is capable of binding to the antibodies. It may be a fragment of glycoprotein C and then binds to types 1 or 2 or to type 1 alone. It may be linked to a label e.g. an enzyme, or to a solid surface. The diagnostic kit may contain unlabeled and labeled complementary antibody. (95pp)
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